

<b>Document Type:</b>	Study Protocol
<b>Official Title:</b>	A multi-center, single-arm, interventional Phase 4 study to evaluate a Treat and Extend regimen of intravitreal aflibercept for treatment of macular edema secondary to central retinal vein occlusion
<b>NCT Number:</b>	NCT02800642
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**A multi-center, single-arm, interventional Phase 4 study to evaluate a Treat and Extend regimen of intravitreal aflibercept for treatment of macular edema secondary to central retinal vein occlusion**

**This protocol version is an integration of the following documents/sections:**

- **Original protocol**, Version 1.0, dated 02 Feb 2016
- **Amendment 01** (global amendment described in Section [15.1](#)) forming integrated protocol Version 2.0, dated 20 Apr 2016

Amendments not included in the consecutive numbering of amendments are local amendments not forming part of this integrated global protocol.

## 1. Title page

**A multi-center, single-arm, interventional Phase 4 study to evaluate a Treat and Extend regimen of intravitreal aflibercept for treatment of macular edema secondary to central retinal vein occlusion**

### CENTERA

Test drug: BAY86-5321/IVT Aflibercept

Study purpose: Interventional

Clinical study phase: 4 Date: 20 Apr 2016

Registration: EudraCT: 2014-003193-17 Version no.: 2.0

Sponsor's study no.: BAY86-5321/17514

Sponsor: **Bayer HealthCare AG, D-51368 Leverkusen, Germany**

Sponsor's medical expert: PPD  
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Wuppertal, Germany  
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Email: PPD

*Please note that Bayer HealthCare AG merges with Bayer AG, an affiliated company within the Bayer Group, effective as of 1st July 2016. Thereby, Bayer HealthCare AG ceases to exist and Bayer AG becomes its legal successor and automatically takes over all of the Bayer HealthCare AG's rights, obligations and liabilities by law. As a result of the above mentioned merger, Bayer AG assumes the role of the sponsor for these trials. Detailed information on the merger will be provided in due time.*

The study will be conducted in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH-GCP) Guidelines, and any applicable regulatory requirements.

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**Signature of the sponsor's medically responsible person**

The signatory agrees to the content of the final integrated clinical study protocol as presented.

Name: PPD

Role: Medical Affairs  
Responsible (MAR)

Date: 26 Apr 2016

Signature: PPD



**Signature of principal investigator**

The signatory agrees to the content of the final integrated clinical study protocol as presented.

Name:

Affiliation:

Date:

Signature:

\_\_\_\_\_

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

## 2. Synopsis – amended

<b>Title</b>	A multi-center, single-arm, interventional Phase 4 study to evaluate a Treat and Extend regimen of intravitreal aflibercept for treatment of macular edema secondary to central retinal vein occlusion
<b>Acronym</b>	CENTERA
<b>Secondary ID</b>	17514
<b>Clinical study phase</b>	4
<b>Study objectives</b>	<p><b><u>Primary:</u></b></p> <ul style="list-style-type: none"> <li>To determine the efficacy and durability (treatment interval) of 2 mg intravitreal (IVT) aflibercept in a Treat and Extend (T&amp;E) regimen over a treatment period of 76 weeks using protocol-defined visual and anatomic criteria in subjects with macular edema secondary to central retinal vein occlusion (CRVO)</li> </ul> <p><b><u>Secondary:</u></b></p> <ul style="list-style-type: none"> <li>To assess the efficacy of IVT aflibercept as measured by visual acuity and anatomic outcomes using spectral domain optical coherence tomography (SD-OCT), and perfusion status using fluorescein angiography (FA)/fundus photography (FP)</li> <li>To assess T&amp;E applied posology of IVT aflibercept (number of injections, length of injection interval)</li> </ul> <p><b><u>Safety:</u></b></p> <ul style="list-style-type: none"> <li>To assess the safety and tolerability of IVT aflibercept in this subject population</li> </ul>
<b>Test drug(s)</b>	
<b>Name of active ingredient</b>	Aflibercept
<b>Dose(s)</b>	2 mg (0.05 mL)
<b>Route of administration</b>	IVT
<b>Duration of treatment</b>	76 weeks
<b>Reference drug</b>	None
<b>Background treatment</b>	None
<b>Indication</b>	Macular edema secondary to CRVO
<b>Diagnosis and main criteria for inclusion/exclusion</b>	Treatment-naïve subjects $\geq$ 18 years of age with center-involved macular edema secondary to CRVO for no longer than 3 months before the first administration of study drug. Subjects must have documented best-corrected visual acuity (BCVA) of Early Treatment Diabetic Retinopathy Study (ETDRS) letter score of 73 to 24 letters (Snellen equivalent of 20/40 to 20/320) in the study eye.

<b>Study design</b>	International, multi-center, prospective, interventional, single-arm cohort, Phase 4 study in adult subjects with a diagnosis of macular edema secondary to CRVO who have previously not been treated with any systemic or IVT anti-vascular endothelial growth factor (VEGF) treatments. Intravitreal aflibercept will be administered to the study eye at specific intervals, with the possibility to extend the treatment interval based on visual and anatomic outcomes as judged by the treating investigator.
<b>Methodology</b>	<p>The study comprises a screening phase (Visit 1: –21 days to baseline), a baseline (Visit 2, Day 1) visit, and a treatment phase (76 weeks).</p> <p>Study treatment with IVT aflibercept will be administered at baseline and at monthly intervals until stabilization of disease. When stability is achieved, the treatment interval can be extended using a T&amp;E approach based on visual and anatomic outcomes as judged by the treating investigator. The initiation phase of the treatment will extend from the first injection until the subject meets criteria for retreatment interval extension or until Week 20.</p> <p>Monitoring will be performed at each injection visit and at Weeks 24, 52, and 76. Starting at Week 8, the stability criteria will be evaluated and the frequency of injections may be adjusted<sup>1</sup> (increased or decreased by 2-week intervals) to maintain stable visual and anatomic outcomes.</p> <p>If the investigator considers the subject to have permanent resolution of macular edema, treatment may be discontinued, but monitoring should be continued with a follow-up visit at a minimum interval of 8 weeks and at all subsequent prescheduled visits (i.e. Weeks 24, 52, and 76). Treatment should be resumed if the retreatment criteria indicate worsening (i.e. at least 1 criterion for deterioration is met).<sup>2</sup></p>
<b>Type of control</b>	None
<b>Number of subjects</b>	160
<b>Variables</b>	<p><b><u>Primary efficacy variables:</u></b></p> <ul style="list-style-type: none"> <li>• The proportion of subjects who gain <math>\geq 15</math> letters in BCVA on the ETDRS chart compared with baseline at Week 76</li> <li>• The proportion of subjects with a mean treatment interval between injections of <math>\geq 8</math> weeks from the last actual visit of the initiation phase to Week 76</li> </ul> <p><b><u>Secondary efficacy variables:</u></b></p> <ul style="list-style-type: none"> <li>• The change in BCVA as measured by the ETDRS letter score from baseline to Weeks 24, 52, and 76</li> <li>• The change in central retinal thickness (CRT) from baseline to Weeks 24, 52, and 76</li> </ul>

<sup>1</sup> Wording changed to clarify that frequency of injections “may be adjusted” to maintain stable visual and anatomic outcomes per Amendment 1, Modification 1 (see Section 15.1.1.1).

<sup>2</sup> Deleted text stating that subjects discontinued from treatment for not benefiting from continued treatment may resume treatment if retreatment criteria indicate worsening per Amendment 1, Modification 2 (Section 15.1.1.2).



	<ul style="list-style-type: none"> <li>• The number of injections from baseline to Week 76</li> <li>• The mean treatment interval between injections from baseline to Week 76</li> <li>• The proportion of subjects who gain <math>\geq 15</math> letters in BCVA on the ETDRS chart compared with baseline at Weeks 24 and 52</li> <li>• The change in retinal perfusion (FA/FP) status from screening/baseline<sup>3</sup> to Weeks 24, 52 and 76</li> <li>• The proportion of subjects with absence of fluid at Weeks 24, 52, and 76</li> </ul> <p><b>Safety variables:</b></p> <ul style="list-style-type: none"> <li>• Number and severity of ocular safety events detected by tonometry, indirect ophthalmoscopy, slit lamp biomicroscopy, and gonioscopy</li> <li>• Number and severity of systemic adverse events (AEs)</li> <li>• Percentage of subjects requiring panretinal photocoagulation (PRP) in the course of the study</li> </ul>
<p><b>Plan for statistical analysis</b></p>	<p>The primary efficacy variable analysis will be conducted on the Full Analysis Set and Per-protocol Set as defined in Section 10.2.</p> <p>The co-primary efficacy variables are as follows:</p> <ul style="list-style-type: none"> <li>• The proportion of subjects who gain <math>\geq 15</math> letters in BCVA on the ETDRS chart compared with baseline at Week 76</li> <li>• The proportion of subjects with a mean treatment interval between injections of <math>\geq 8</math> weeks from the last actual visit of the initiation phase to Week 76</li> </ul> <p>Secondary and exploratory variables will be evaluated by means of 95% confidence intervals based on appropriate statistical methodology (either McNemar or t-distribution based).</p> <p>For other efficacy variables, with regard to proportion of responder-based variables, subjects discontinued until the respective time point will be considered as non-responders (if no proof of permanent resolution of macular edema exists).</p> <p>For change from baseline-based variables, missing data will be imputed by means of the last observation carried forward method. Sensitivity analyses for these variables will be provided, based on the multiple imputation method as outlined in the statistical analysis plan. In addition, observed case-based sensitivity analyses will be provided for secondary efficacy variables.</p>

<sup>3</sup> Clarified that assessment of secondary variable of change in retinal perfusion status will include screening/baseline combined visit per Amendment 1, Modification 3 (see Section 15.1.1.3).



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## List of abbreviations

2Q4	2 mg IVT injection every of 4 weeks
AE	Adverse event
AMD	Age-related macular degeneration
APTC	Antiplatelet Trialists' Collaboration
ATE	Arterial thrombotic events
BCVA	Best-corrected visual acuity
BRVO	Branch retinal vein occlusion
CRO	Clinical research organization
CRT	Central retinal thickness
CRVO	Central retinal vein occlusion
eCRF	Electronic case report form
EDC	Electronic data capture
e.g.	For example ( <i>exempli gratia</i> )
ERG	Electroretinogram
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein angiography
FP	Fundus photography
GCP	Good Clinical Practice
ICF	Informed consent form
i.e.	That is ( <i>id est</i> )
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IRB	Institutional Review Board
ISCEV	The International Society for Clinical Electrophysiology of Vision
IVT	Intravitreal
IxRS	Interactive voice/web response system
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
OCT	Optical coherence tomography
PASS	Power Analysis and Sample Size
PRN	As needed ( <i>pro re nata</i> )
PRP	Panretinal photocoagulation
RAPD	Relative afferent pupillary defect
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD-OCT	Spectral domain optical coherence tomography
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
T&E	Treat and Extend
US	United States
VEGF	Vascular endothelial growth factor

### 3. Introduction

#### Background

Retinal venous occlusive disease is an important cause of vision loss, particularly in patients with associated chronic macular edema (1). The 2 major categories are central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).

Aflibercept is a potent, specific inhibitor of vascular endothelial growth factor (VEGF) with a high affinity for all isoforms of VEGF and placental growth factor. To date, intravitreal (IVT) aflibercept has been approved as a treatment for macular edema secondary to CRVO, neovascular age-related macular degeneration (AMD), diabetic macular edema, and macular edema secondary to BRVO and CRVO in the United States (US), European Union (EU), Japan, and other countries; for myopic choroidal neovascularization in Japan and other countries; and for diabetic retinopathy in patients with diabetic macular edema in the US.

Further details are provided in the applicable Summary of Product Characteristics (SmPC) (2)<sup>4</sup>.

#### Central retinal vein occlusion

Central retinal vein occlusion results 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 VEGF, which can lead to vascular permeability, macular edema, retinal hemorrhage, and neovascularization. Patients with macular edema secondary to CRVO lose visual acuity, and the visual prognosis, if untreated, is frequently poor. As a result of the role that VEGF plays in the pathology of macular edema secondary to CRVO, VEGF has become an important drug target in treatment strategies.

Central retinal vein occlusion affects men and women equally and most often occurs in persons over the age of 65 years. Population-based studies report the prevalence of macular edema secondary to CRVO at 0.1% to 0.4%. While it is usually unilateral, it is estimated that up to 7% of persons may develop a similar macular edema secondary to CRVO in the fellow eye within 5 years from initial diagnosis (3, 4).

#### Development program of intravitreal aflibercept in macular edema secondary to CRVO

The Phase 3 program for IVT aflibercept in macular edema secondary to CRVO included 2 pivotal studies, Study VGFT-OD-0819 (COPERNICUS) and Study 14130 (GALILEO) conducted in subjects with macular edema secondary to CRVO. Subjects in COPERNICUS were followed for a total of 2 years (i.e. 100 weeks), while subjects in GALILEO were followed for 18 months (i.e. 76 weeks). In both studies, subjects received either IVT aflibercept or sham injections every 4 weeks from baseline to Week 20. The primary efficacy variable for both studies was the proportion of subjects who gained  $\geq 15$  letters in best-corrected visual acuity (BCVA) at the Week 24 time point compared with baseline. In both studies, all assessments were made at Week 24 (the primary variable) before treatment was administered. Both Phase 3 studies fully met the stated primary variable and an integrated

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<sup>4</sup> Reference to SmPC applied per Amendment 1, Modification 4 (see Section 15.1.1.4).

analysis confirmed the primary variable results of COPERNICUS and GALILEO. In both studies, the comparison of IVT aflibercept to sham treatment showed statistical significance in favor of IVT aflibercept and, thus, demonstrated the superiority of IVT aflibercept. In COPERNICUS, 56.1% of subjects treated with IVT aflibercept every 4 weeks gained  $\geq 15$  letters in visual acuity at Week 24, versus 12.3% in the sham group. Similarly, in GALILEO, 60.2% of subjects treated with IVT aflibercept every 4 weeks gained  $\geq 15$  letters in visual acuity at Week 24, versus 22.1% in the sham group. The superiority of IVT aflibercept treatment every 4 weeks was confirmed in all supportive and sensitivity analyses. The superiority of IVT aflibercept was also supported by the results for the secondary variables of change in BCVA letter score (baseline to Week 24) and reduction in central retinal thickness (CRT) (baseline to Week 24).

A total of 317 subjects treated with at least 1 dose of IVT aflibercept constituted the safety population in the two Phase 3 studies with up to 100 weeks exposure. Intravitreal aflibercept was generally well tolerated in clinical trials, and there is little potential for systemic drug accumulation. Serious adverse reactions related to the injection procedure occurred in 3 out of 2,728 injections with IVT aflibercept and included endophthalmitis, cataract, and vitreous detachment. The most common adverse reactions (in at least 5% of subjects treated with IVT aflibercept) were conjunctival hemorrhage (15.8%), increased intraocular pressure (IOP) (12.9%), eye pain (12.6%), vitreous detachment (6.9%), vitreous floaters (5.7%), increased lacrimation (5.0%), and ocular hyperemia (5.0%).

Additional information is provided in the applicable SmPC.

Overall, IVT aflibercept is an effective and generally well-tolerated agent that extends the options available for the treatment of macular edema secondary to CRVO.

## Rationale of the study

### Treat and Extend

The use of anti-VEGF agents for macular edema secondary to CRVO has become the standard of care.

To investigate the possibility of extending the treatment interval after the initial Q4 treatment phase, both pivotal Phase 3 studies (COPERNICUS and GALILEO) included an as needed (*pro re nata*) (PRN) dosing regimen that began after the first 6 months of treatment (i.e. began at the Week 24 visit after all assessments for the primary variable had been made).

Post-hoc analyses of the different dosing subgroup assessments (number of IVT aflibercept injections and interval between IVT aflibercept injections) in the two Phase 3 studies suggested some de-stabilization of the disease and return of signs and symptoms with PRN dosing. While the deterioration may be rather minor after only 6 months (i.e. the PRN phase in these studies), it is likely to become more significant over the expected long-term treatment duration needed by patients with macular edema secondary to CRVO. These data, therefore, support the recommendation that subjects be treated according to a more proactive dosing regimen rather than a reactive dosing regimen (e.g. PRN) based on deterioration in visual and/or morphology variables.



Furthermore, frequent dosing for anti-VEGFs has introduced a burden of illness on patients and caregivers as well as capability constraints on physicians in practice. Physicians have developed a practicing trend toward individualizing treatment to reduce the burden and minimize reimbursement issues and healthcare costs. The current proactive individualized treatment gaining momentum with practicing physicians is referred to as Treat and Extend (T&E).

In the T&E dosing paradigm, the subject is injected every visit and intervals for follow-up treatments are typically adapted in incremental intervals according to the response to treatment.

The T&E regimen for neovascular AMD was initially described by Spaide in 2007 (5) and applied in several studies since then (6, 7, 8, 9, 10, 11, 12); however, no large-scale studies have examined the use of IVT aflibercept in a T&E regimen for macular edema secondary to CRVO or other indications.

In February 2015, the macular edema secondary to CRVO indication in the EU SmPC for IVT aflibercept was expanded to retinal vein occlusion (RVO), based on data from the VIBRANT study (Phase 3 study in patients with macular edema secondary to BRVO), and was updated to reflect a T&E approach to extend treatment intervals:

“After the initial injection, treatment is given monthly. The interval between two doses should not be shorter than 1 month. If visual and anatomic outcomes indicate that the patient is not benefiting from continued treatment, Eylea should be discontinued. Monthly treatment continues until maximum visual acuity is achieved and/or there are no signs of disease activity. Three or more consecutive, monthly injections may be needed. Treatment may then be continued with a T&E regimen with gradually increased treatment intervals to maintain stable visual and/or anatomic outcomes, however there are insufficient data to conclude on the length of these intervals. If visual and/or anatomic outcomes deteriorate, the treatment interval should be shortened accordingly. The monitoring and treatment schedule should be determined by the treating physician based on the individual patient’s response. Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography [OCT] or fluorescein angiography [FA])” (2).

Treat and Extend has emerged as a preferred regimen for many treating physicians as it is a proactive approach to individualized treatment, monitoring frequency, and intervals. This concept aims to maintain maximized visual and anatomic outcomes gained in the initiation phase of treatment by proactively treating the subject at each visit and minimizing the burden of intervention by extending the treatment interval (if extension criteria are met) and thus limiting visits, monitoring, and injections.

However, there are no studies available that address the question of what are useful intervals for treating and monitoring, how do they differ among subjects, and how are retreatment criteria applied to achieve long-term desirable outcomes in real world practice.

Furthermore, previous studies identified the importance of perfusion status (e.g. as a prognostic variable) in CRVO but assessment of perfusion status was often limited to standard angiography of the central sections of the retina (GALILEO) (13,14).

This study aims to evaluate the efficacy, durability, posology, and safety of the T&E regimen with IVT aflibercept in subjects with macular edema secondary to CRVO.

In addition, this study will explore emerging imaging methods, including non-invasive and wide-angle assessment of perfusion status of the affected eye.

### **Benefit-risk assessment**

Injection of IVT aflibercept in this study of subjects with macular edema secondary to CRVO is justified and supported by the drug's safety and tolerability profile known from previous registration studies investigating IVT aflibercept in macular edema secondary to CRVO and other indications. The beneficial effect on visual acuity in patients with macular edema secondary to CRVO has previously been demonstrated, both with IVT aflibercept treatment and with other anti-VEGF therapy.

Due to the low systemic level of aflibercept after IVT injection, the likelihood of adverse events (AEs) other than ocular is very low and systemic pharmacodynamic effects such as blood pressure changes are unlikely. Proteinuria and hypertension are potential systemic effects from intravenous or subcutaneous administration of this class of drug; however, the low systemic blood levels observed in previous IVT studies suggest that direct IVT injection, at the dose levels proposed for this study, are not expected to have clinically significant systemic effects (15,16). In addition, arterial thromboembolic events (ATEs) are AEs potentially related to systemic VEGF inhibition. The risks associated with IVT aflibercept observed in the Phase 3 studies are thought to be similar to those of IVT administration of pegaptanib sodium and ranibizumab.

Given its higher affinity for VEGF compared with ranibizumab and its ability to be administered at higher doses, IVT aflibercept may provide a clinical benefit with the potential for a longer dosing interval that is equivalent to and potentially greater than that of ranibizumab (17,18,19). Given that the subjects to be enrolled in this study generally have advanced blinding disease with a poor prognosis, and given the potential for IVT aflibercept to provide as good or potentially better therapy than ranibizumab without known increased risk, it is reasonable to assume that the potential benefit of IVT aflibercept, a highly potent therapeutic agent, outweighs any attendant short-term risks for subjects participating in this study.

## **4. Study objectives**

### **Primary objective**

- To determine the efficacy and durability (treatment interval) of 2 mg IVT aflibercept in a T&E regimen over a treatment period of 76 weeks using protocol-defined visual and anatomic criteria in subjects with macular edema secondary to CRVO

## Secondary objectives

- To assess the efficacy of IVT aflibercept as measured by visual acuity and anatomic outcomes using spectral domain optical coherence tomography (SD-OCT), and perfusion status using FA/fundus photography (FP)
- To assess T&E applied posology of IVT aflibercept (number of injections, length of injection interval)

## Safety objective

- To assess the safety and tolerability of IVT aflibercept in this subject population

## Exploratory objectives (only at those sites with equipment available)

- To evaluate wide-field (angle) FA for utility in assessing perfusion status in the periphery of the retina, which is currently not evaluable using traditional FA, and examination of morphological changes related to disease progression in CRVO
- To evaluate OCT angiography for dynamic assessment of retinal capillary perfusion status
- To evaluate full-field electroretinography (ERG) for functional assessment of retinal ischemia
- To evaluate relative afferent pupillary defect (RAPD) appearance or changes related to disease progression in CRVO

## 5. Study design – amended

### Design overview

This is an international, multi-center, prospective, interventional, single-arm cohort, Phase 4 study in adult subjects with a diagnosis of macular edema secondary to CRVO who have previously not been treated with any systemic or IVT anti-VEGF treatments.

The diagnosis and treatment decision is made at the discretion of the attending investigator. The investigator will have made the choice of treatment (IVT aflibercept) as well as the decision to use IVT aflibercept according the core SmPC principles (or other applicable product information) prior to enrolling the subject in this study.

One-hundred sixty subjects will be enrolled in this international study.

The initial screening visit must be within the enrollment period in the respective country (i.e. no retrospective inclusion). Subjects must give written informed consent prior to any data documentation. Subjects will receive the first study treatment at the baseline visit on Day 1.<sup>5</sup>

The treatment phase comprises an initiation phase followed by a T&E phase. During the T&E phase, all subjects will be treated with the study drug IVT aflibercept using a T&E approach.

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<sup>5</sup> “Screening and baseline need to be separate visits in order to confirm the inclusion/exclusion criteria” removed for consistency with rest of protocol that screening and baseline visits can be combined per Amendment 1, Modification 5 (see Section 15.1.1.5).





Subjects will be followed for a time period of 76 weeks or until follow-up is no longer possible.<sup>6</sup> The treatment period for each subject is scheduled to be 76 weeks. Subjects may receive treatment of their underlying disease at their physician's discretion at Week 76 after the end-of-study visit and the assessments for all variables are completed. For patients that have received a study drug injection less than 30 days before the end-of-study visit, an additional AE follow-up phone call will be scheduled 30 days after the last study drug injection. Therefore, the study duration will be 76 weeks plus the screening period and potential AE follow-up.

This study comprises a screening period of up to 21 days and a treatment period of 76 weeks. There will be prescheduled visits at baseline, Weeks 24, 52, and 76 (end-of-study visit).<sup>7</sup> Other visits between baseline and Week 76 will depend on the applied posology of IVT aflibercept and the monitoring schedule for each subject. A  $\pm 7$ -day window will be allowed for all post-baseline visits.<sup>8</sup>

Subjects treated with a deviation from the proposed regimen will continue to be assessed according to the posology interval of the subject.

Under this protocol, FA/FP evaluations will be conducted in both eyes at screening/baseline, and in the study eye only at Weeks 24, 52, and 76, and the early termination visit (and in the fellow eye if there are signs of vein occlusion). Best-corrected visual acuity and SD-OCT will be conducted in both eyes at every visit. Wide-field FA, OCT angiography, and full-field ERG may be conducted, at selected study sites, in both eyes at baseline and in the study eye only at Weeks 24, 52, and 76, and the early termination visit (and in the fellow eye if there are signs of vein occlusion). However, the treating investigator may perform FA/FP, wide-field FA, OCT angiography, or full-field ERG at other times during the 76 weeks of study treatment based on his/her medical judgment and standard of care.<sup>9</sup>

### Primary, secondary, safety, and exploratory variables

Co-primary efficacy variables:

- The proportion of subjects who gain  $\geq 15$  letters in BCVA on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart compared with baseline at Week 76
- The proportion of subjects with a mean treatment interval between injections of  $\geq 8$  weeks from the last actual visit of the initiation phase to Week 76

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<sup>6</sup> Subjects will continue to be followed to Week 76 or until follow-up is no longer possible per Amendment 1, Modification 6 (see Section 15.1.1.6).

<sup>7</sup> Removed sentence that visit schedules at Weeks 24, 52, and 76 may deviate by  $\pm 7$  days sentence to clarify that a  $\pm 7$ -day window will be allowed for all post-baseline visits per Amendment 1, Modification 7 (see Section 15.1.1.7).

<sup>8</sup> Added sentence to clarify that a  $\pm 7$ -day window will be allowed for all post-baseline visits per Amendment 1, Modification 7 (see Section 15.1.1.7).

<sup>9</sup> Added wide-field FA and OCT angiography to the examinations that may be performed at other times during the study based on the investigator's medical judgment and standard of care per Amendment 1, Modification 8 (see Section 15.1.1.8).

## Secondary efficacy variables:

- The change in BCVA as measured by the ETDRS letter score from baseline to Weeks 24, 52, and 76
- The change in CRT from baseline to Weeks 24, 52, and 76
- The number of injections from baseline to Week 76
- The mean treatment interval between injections from baseline to Week 76
- The proportion of subjects who gain  $\geq 15$  letters in BCVA on the ETDRS chart compared with baseline at Weeks 24 and 52
- The change in retinal perfusion (FA/FP) status from screening/baseline<sup>10</sup> to Weeks 24, 52, and 76
- The proportion of subjects with absence of fluid at Weeks 24, 52, and 76

## Safety variables:

- Number and severity of ocular safety events detected by tonometry, indirect ophthalmoscopy, slit lamp biomicroscopy, and gonioscopy
- Number and severity of systemic AEs
- Percentage of subjects requiring panretinal photocoagulation (PRP) in the course of the study

## Exploratory variables:

- Perfusion status of the retina assessed by wide-field FA at screening/baseline,<sup>11</sup> Weeks 24, 52, and 76
- OCT angiography measures for assessing perfusion status of the retina and examination of morphological changes related to disease progression in CRVO at baseline, Weeks 24, 52, and 76
- Full-field ERG assessments at baseline, Weeks 24, 52, and 76
- Status of RAPD at baseline, Weeks 24, 52, and 76

**Justification of the design**

The primary objective of this single-arm unmasked study is to determine the efficacy and durability (treatment interval) of 2 mg IVT aflibercept in a T&E regimen over a treatment period of 76 weeks using protocol-defined visual and anatomic criteria in subjects with macular edema secondary to CRVO.

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<sup>10</sup> Clarified that assessment of secondary variable of change in retinal perfusion status will include screening/baseline combined visit per Amendment 1, Modification 3 (see Section 15.1.1.3).

<sup>11</sup> Clarified that exploratory variable of perfusion status of the retina will be assessed by wide-field FA at screening/baseline per Amendment 1, Modification 9 (see Section 15.1.1.9).



### ***Single-arm design***

The single-arm design using T&E for all patients was chosen since substantial data is available for comparison from previous macular edema secondary to CRVO studies that used fixed dosing followed by PRN dosing. The Phase 3 program for IVT aflibercept in macular edema secondary to CRVO included 2 pivotal studies (COPERNICUS and GALILEO) combining fixed dosing and PRN dosing. Subjects in the COPERNICUS study were followed for a total of 2 years (i.e. 100 weeks), while subjects in the GALILEO study were followed for 18 months (i.e. 76 weeks). The prespecified time points in both studies were the same as in CENTERA (baseline, Weeks 24, 52, and 76), and the variables and study populations were similar to that of CENTERA.

### ***Treat and Extend***

CENTERA is the first Phase 4 study to investigate a proactive T&E regimen with IVT aflibercept for the treatment of macular edema secondary to CRVO. Efficacy observations in the 2 previous studies (COPERNICUS and GALILEO) suggest some destabilization or reactivation of disease with the switch to PRN dosing. A more proactive regimen of treating patients (T&E) at each visit and individualizing the treatment interval to maintain visual and anatomic stability may provide additional benefit. Based on advice received in expert meetings and based on the two Phase 3 studies, a set of visual and anatomic (OCT based) retreatment criteria were defined. Therefore, CENTERA will explore treatment with IVT aflibercept according to a proactive T&E dosing regimen with adjustment of treatment intervals based on the monitoring of stability by protocol-defined visual and/or anatomical outcomes.

### ***Variables***

The primary and secondary variables in CENTERA were studied in previous Phase 3 RVO trials. CENTERA will also incorporate several exploratory variables to add to the understanding of pathology and treatment-related changes of macular edema secondary to CRVO. Ischemic CRVO is defined by the appearance of neovascularization on the surface of the iris (rubeosis iridis) or by FA-confirmed areas of retinal ischemia larger than 10 disc areas. The latter has been assessed in clinical Phase 3 trials, but this dichotomized variable is not fully satisfactory to characterize perfusion status in the affected eye. In this study, in addition to the standard FA assessment, the following 2 imaging and 1 functional assessment will be applied at selected sites where instrumentation and technical competence are available:

- Wide-field (angle) FA will allow for the assessment of perfusion status in the periphery of the retina, which is currently not evaluable using traditional FA but seems to be affected in CRVO
- OCT angiography for dynamic assessment of retinal capillary perfusion status at baseline, which does not require a contrast agent to evaluate dynamic changes
- Full-field ERG will allow for functional assessment of retinal ischemia

The combination of these methods will enable a comprehensive assessment of perfusion status, including within the periphery and functional changes. The comparison of methodology and results may yield important insights for future clinical studies.

### End of study

The end of the study as a whole will be reached as soon as the last visit of the last subject, including safety follow-up<sup>12</sup> is reached in all centers in all participating countries (EU and non-EU).

### Primary completion of study

The primary completion event for this study is the final study visit at Week 76, including the mandatory safety follow-up contact.<sup>13</sup>

## 6. Study population – amended

Eligibility for participation in this study will be based on the inclusion/exclusion criteria.

All inclusion/exclusion criteria will be assessed during the screening phase, and the subject must sign the informed consent form (ICF) before any of the inclusion/exclusion criteria are assessed.

In order to be enrolled into this study, a subject must meet ALL of the eligibility criteria.<sup>14</sup>

Only 1 eye will be designated as the study eye. For subjects who meet eligibility criteria in both eyes, the eye with the worse visual acuity will be selected as the study eye. If both eyes have equal visual acuity, the eye with the clearest lens and ocular media, as determined by the investigator, will be selected. If there is no objective basis for selecting the study eye, factors such as ocular dominance, other ocular pathology, and subject preference should be considered in making the selection. The fellow eye will be assessed as outlined in Section 9.

### 6.1 Inclusion criteria

1. Signed informed consent.
2. Center-involved macular edema secondary to CRVO for no longer than 3 months (at the screening visit it should be ensured that the subjects will comply with the criterion of  $\leq 3$  months since onset of macular edema at their scheduled baseline visit).
3. Adult subjects diagnosed with macular edema secondary to CRVO who are scheduled to be treated with IVT aflibercept as per investigator's routine treatment practice with the intent to use a T&E regimen after initial dosing.

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<sup>12</sup> Clarified that the safety follow-up period is included in the definition of the end of the study per Amendment 1, Modification 10 (see Section 15.1.1.10).

<sup>13</sup> Clarified that the mandatory safety follow-up contact is included in the definition of completion of the final study visit per Amendment 1, Modification 11 (see Section 15.1.1.11).

<sup>14</sup> Removed sentence that assessment based on OCT assessment, BCVA, and FA and FP will be repeated at the baseline visit per Amendment 1, Modification 12 (see Section 15.1.1.12).



4. Treatment-naïve subjects for macular edema secondary to CRVO.
5. Men and women  $\geq 18$  years of age.
6. Documented BCVA of ETDRS letter score of 73 to 24 letters (Snellen equivalent of 20/40 to 20/320) in the study eye.
7. Subject is willing, committed, and able to return for all clinic visits and complete all study-related procedures.
8. Women and men of reproductive potential<sup>15</sup> must agree to use adequate contraception when sexually active. This applies for the time period between signing of the ICF and 3 months after the last administration of study drug. The definition of adequate contraception will be based on the judgment of the investigator and on local requirements. Acceptable methods of contraception include, but are not limited to, (i) condoms (male or female) with or without a spermicidal agent; (ii) diaphragm or cervical cap with spermicide; (iii) intra-uterine device; (iv) hormone-based contraception. Subjects must agree to utilize two reliable and acceptable methods of contraception simultaneously.
9. Negative pregnancy test (women of childbearing potential only<sup>15</sup>).

## 6.2 Exclusion criteria – amended

1. Previous (within 12 months) or concomitant participation in another clinical study with investigational medicinal product(s).
2. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site).
3. Previous PRP or macular laser photocoagulation in the study eye.
4. Any prior or concomitant ocular treatment (e.g. anti-VEGF therapy, corticosteroids) in the study eye for macular edema secondary to RVO, except dietary supplements or vitamins prior to inclusion in the study. Intraocular anti-VEGF treatment is permitted for the treatment of diseases of fellow eye except for those that are specifically excluded.
5. Prior systemic anti-VEGF or corticosteroid therapy, investigational or approved, within the last 3 months before the first dose in the study.
6. Previous use of intraocular corticosteroids in the study eye at any time or use of periocular corticosteroids in the study eye within 12 months prior to Day 1.
7. Any active intraocular, extraocular, and periocular inflammation or infection in either eye within 4 weeks of screening.
8. Any history of allergy to povidone iodine.
9. Known serious allergy to the fluorescein sodium for injection in angiography.

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<sup>15</sup> Women of reproductive or childbearing potential: Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. (footnote to text; not a modification)



10. Presence of any contraindications indicated in the EU commission/locally approved label for IVT aflibercept: hypersensitivity to the active substance IVT aflibercept or to any of the excipients; active or suspected ocular or periocular infection; active severe intraocular inflammation.
11. A history of vitreoretinal surgery in the study eye prior to Day 1 (Visit 2) or anticipated within the 18 months following Day 1.
12. Iris neovascularization, neovascularization or fibrosis of the iridocorneal angle, or vitreous hemorrhage in the study eye.
13. History of vitreomacular traction in either the study eye or the fellow eye evident by biomicroscopic or OCT assessment that is considered by the investigator to affect central vision significantly.
14. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
15. Any history of macular hole of stage 2 and above in the study eye.
16. Prior trabeculectomy or other filtration surgery in the study eye.
17. Uncontrolled glaucoma (defined as IOP more than 25 mm Hg despite treatment with antiglaucoma medication) in the study eye.
18. Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of an yttrium aluminum garnet posterior capsulotomy) in the study eye.
19. Previous therapeutic radiation in the region of the study eye.
20. History of corneal transplant or corneal dystrophy in the study eye.
21. Significant media opacities, including cataract, in the study eye that interfere with visual acuity or FP.
22. History or clinical evidence of diabetic macular edema, AMD (neovascular AMD or geographic atrophy), BRVO, or any retinal vascular disease other than macular edema secondary to CRVO in either eye.<sup>16</sup>
23. Any history of uveitis in either eye.
24. Presence of scleromalacia in either eye.
25. Pregnancy or breastfeeding.

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<sup>16</sup> Types of AMD defined per Amendment 1, Modification 13 (see Section 15.1.1.13).

## 6.3 Withdrawal of subjects from the study

### 6.3.1 Withdrawal – amended

#### Withdrawal criteria

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

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.

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

- If, in the investigator's opinion, the subject is not benefiting from continued treatment or continuation of the study would be harmful to the subject's well-being.
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening failure" or "dropout" as specified below.

#### Screening failure

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see below) is regarded a "screening failure."

Restarting the defined set of screening procedures to enable the "screening failure" subject's participation at a later time point is not allowed, with the following exceptions:

- The subject had successfully passed the screening procedures but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The inclusion/exclusion criteria preventing the subject's initial attempt to participate have been changed (via protocol amendment).
- The reason for the screening failure was subsequently resolved (e.g. elevated IOP decreases, inflammation or infection resolves) within 30 days.<sup>17</sup>

However, if a subject fails screening (i.e. does not meet all inclusion criteria or meets 1 or more of the exclusion criteria),<sup>18</sup> the subject can be re-screened 1 time, if the reason(s) for the screening failure is(are) resolved.

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<sup>17</sup> Added that subjects may be rescreened if reason for initial screening failure was resolved within 30 days of initial screening per Amendment 1, Modification 14 (see Section 15.1.1.14).

<sup>18</sup> Removed examples of exclusion criteria per Amendment 1, Modification 15 (see Section 15.1.1.15).



In any case, the investigator has to ensure that the repeated screening procedures do not expose the subject to an unjustifiable health risk. In addition, for re-screening, the subject has to re-sign the ICF, even if it was not changed after the subject's previous screening.

## Dropout

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already received IVT aflibercept.

## General procedures

In all cases, the reason for withdrawal must be recorded in the electronic case report form (eCRF) and in the subject's medical records.

The subject may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12 (premature termination of the study).

### 6.3.2 Replacement

Withdrawn subjects will not be replaced.

## 6.4 Subject identification

The subject number is a 9-digit number consisting of a 2-digit country code, a 3-digit center number, and a 4-digit subject number (within the center).

Once assigned to a subject, the subject identification number will not be re-used.

## 7. Treatments

### 7.1 Treatments to be administered

This study is an open-label single-arm study. The recommended dose for IVT aflibercept is 2 mg equivalent to 50  $\mu$ L. All subjects will be treated with the study drug IVT aflibercept using a T&E approach. The sponsor will provide study drug.

#### 7.1.1 Treat and Extend treatment visits – amended

Study treatment with IVT aflibercept will be administered at baseline and at monthly intervals until stabilization of disease. When stability is achieved, the treatment interval can be extended based on visual and anatomic outcomes as judged by the treating investigator.

Criteria for determination of retreatment intervals are summarized in Section 7.1.3 below. If visual and anatomic outcomes indicate that the subject is not benefiting from continued treatment, IVT aflibercept should be discontinued.

The initiation phase of the treatment will extend from the first injection until the subject meets retreatment interval extension criteria as summarized in Section 7.1.3.

Monitoring will be performed at each injection visit and at Weeks 24, 52, and 76. Starting at Week 8, the retreatment interval will be determined as described in Section 7.1.3 and the frequency of injections may be adjusted<sup>19</sup> (increased or decreased by 2-week intervals) to maintain stable visual and anatomic outcomes.

### 7.1.2 Stability criteria – amended

At every injection visit, the stability of the patient's condition will be evaluated. To be considered stable, the condition must fulfill the following criteria:

- No new cysts on OCT
- BCVA within a  $\pm 5$  letter “stability corridor” defined by:
  - No more than 5 letters gain since the last or second to last visit<sup>20</sup>
  - No more than 5 letters loss from best previous BCVA at any visit
- CRT within a  $\pm 20\%$  “stability corridor” defined by:
  - No more than 20% thickness reduction since the last or second to last visit<sup>21</sup>
  - No more than 20% thickening from best previous CRT at any visit

Values of BCVA and CRT outside these “stability corridors” will be considered as “improvements” for higher BCVAs and lower CRTs and “deteriorations” for lower BCVAs and higher CRTs.

### 7.1.3 Determination of the next retreatment interval (extension/maintenance/reduction)

The initiation phase of the treatment will extend from the first injection until the subject meets all stability criteria as summarized in Section 7.1.2 or until Week 20 (whichever occurs first).

At every injection visit, the investigator will enter into the eCRF the measured BCVA and CRT. The eCRF will then suggest a stability status of the patient's condition (stable / improving / deteriorating) for each of the 3 stability criteria and propose a recommended retreatment interval (based on the below algorithm) which the investigator must confirm.

#### Algorithm for determination of the retreatment interval

- *If the condition is stable (all stability criteria met):*
  - Treatment interval extended by 2 weeks
- *If the condition is improving (No new cysts and improvement in at least one of the disease activity criteria [BCVA or CRT] while the other is improving or stable):*

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<sup>19</sup> Wording changed to clarify that frequency of injections “may be adjusted” to maintain stable visual and anatomic outcomes per Amendment 1, Modification 1 (see Section 15.1.1.1).

<sup>20</sup> Text reworded from “previous last visit” to “second to last visit” per Amendment 1, Modification 16 (see Section 15.1.1.16).

<sup>21</sup> Text reworded from “previous last visit” to “second to last visit” per Amendment 1, Modification 16 (see Section 15.1.1.16).



- Treatment interval maintained
- *If the condition is deteriorating (New cysts and/or deterioration in at least one of the other disease activity criteria [BCVA or CRT]):*
  - Treatment interval reduced by 2 weeks

Injections will not be administered more frequently than every 4 weeks (minimum retreatment interval).

#### **7.1.4 Deviation from the recommended retreatment interval**

Deviation from the recommended treatment regimen or retreatment interval, if required for the well-being of the subject, will be recorded in the eCRF with a detailed clinical explanation of the reasons for deviation from protocol-defined dosing.

#### **7.1.5 Discontinuation of treatment**

If it is determined by the investigator (in the investigator's best judgment) that the subject is not benefiting from continued treatment, the subject may be withdrawn from the study (see Section 6.3.1).

If the investigator considers permanent resolution of macular edema, treatment may be withheld, but monitoring should be continued with a follow-up visit at a minimum interval of 8 weeks and at all subsequent prescheduled visits (i.e. Weeks 24, 52, and 76). Treatment should be resumed if the retreatment criteria indicate worsening (i.e. at least 1 criterion for deterioration is met).

### **7.2 Identity of study treatment**

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor's study file.

The study drug, IVT aflibercept, will be manufactured by Bayer Pharma AG, Berlin, Germany and supplied by the sponsor in sealed, single-use, sterile 2-mL vials, each with a final extractable volume of 0.10 mL. Details of the study drug are provided in [Table 7-1](#).



**Table 7-1: Investigational Test Product**

Name	Dose	Concentration	Volume	Formulation	Composition
BAY 86-5321/ IVT aflibercept	2 mg	40 mg/mL	Injected: 0.05 mL	Solution for intravitreal injection	- 40 mg aflibercept/mL - 5% sucrose - 10 mM sodium phosphate - 0.03% polysorbate 20 - 40 mM sodium chloride (NaCl) - Water for injection

### 7.3 Treatment assignment

Subjects enrolled in this single-arm study will receive treatment at the discretion of the investigator. However, as this study has the aim to investigate the T&E regimen with IVT aflibercept, the expectation is that the investigator and subject will apply the T&E regimen as described in this study protocol if no medical or other reasons indicate otherwise.

### 7.4 Dosage and administration – amended

The volume of injection will be 50 µL (0.05 mL) for the 2 mg dose of IVT aflibercept. The study drug will be withdrawn using aseptic technique through an 18-gauge filter needle attached to a 1-mL syringe. The filter needle will be discarded after withdrawal of the vial contents and should not be used for IVT injection. The filter needle should be replaced with a sterile 30-gauge needle for the IVT injection. The contents in the syringe should be expelled until the plunger is aligned with the line that marks 0.05 mL on the syringe.

Prior to administration, visually inspect the solution for injection. Do not use the vial if particulates, cloudiness, or discoloration are visible.

Vials of IVT aflibercept are to be stored at 2°C to 8°C. Do not freeze. Keep the vial in the outer carton to protect it from light. Prior to usage, the unopened vial of IVT aflibercept may be stored at room temperature (below 25°C/77°F) for up to 24 hours. After opening the vial, procedures must take place under aseptic conditions.<sup>22</sup>

Intravitreal aflibercept will be administered to the study eye. For the dosing schedule and planned duration, see Section 7. The study drug injection procedure is detailed in Appendix 16.1.

### 7.5 Drug logistics and accountability – amended

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practice requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/clinical research organization [CRO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a

<sup>22</sup> Removed text stating that dose must be administered within 2 hours of start of dose preparation per Amendment 1, Modification 17 (see Section 15.1.1.17).



complete record of batch numbers and expiry dates can be found in the sponsor study file; the site-relevant elements of this information will be available in the investigator site file.

Vials of IVT aflibercept are to be stored at 2°C to 8°C. The drug must not be frozen. Before usage, the unopened IVT aflibercept vial may be stored at room temperature (below 25°C/77°F) for up to 24 hours. Keep the vial in the outer carton to protect it from light. The temperature in the storage refrigerator has to be measured daily on working days with a minimum/maximum thermometer (continuous temperature monitoring is also allowed). Records of actual storage conditions (i.e. temperature log) at the study site must be maintained. These must include a record of the dates on which the storage refrigerator was checked, the initials of the person checking the temperature, and the temperature at that time.

The responsible site personnel will confirm receipt of study drug via interactive voice/web response system (IxRS) on the day of receipt or the earliest possible time point. The personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return, and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Written instructions on medication destruction will be made available to affected parties as applicable.

The physician or designated medical or pharmacy personnel handling the drug product are responsible for the accountability of all used, partially used, and unused study drug. Drug accountability records must be kept current and should contain the dates, quantities, kit numbers, and batch numbers (or lot numbers) of study drug received by the investigator, dispensed or administered to specified subjects, disposed of at the site (disposal at the site may occur only with a sponsor or designee approval or by a specified designee).<sup>23</sup> Drug accountability will be overseen by study site personnel. All inventories, along with shipment receipts, shipment temperature recordings (if applicable), storage temperature logs, pharmacy dose preparation logs, and IxRS confirmation reports must be made available for inspection by study site personnel. At the conclusion of the study, photocopies of all drug accountability records will be provided by each site to the sponsor.

### 7.5.1 Packaging

All IVT aflibercept study medication will be packaged with a kit number. Each IVT aflibercept treatment kit will contain 40 mg/mL IVT aflibercept in a sealed, single use, sterile 2-mL vial with a final extractable volume of 0.10 mL. In accordance with local regulations, each kit will contain one 18-gauge filter needle.

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<sup>23</sup> Added that sponsor designee may approve disposal of drug and removed that study drug may be returned to the sponsor for disposal per Amendment 1, Modification 18 (see Section 15.1.1.18).

### 7.5.2 Labeling

The study-drug label will generally contain the following information according to regulations applicable to the study countries. Additional information, as required, may be added to the study-drug label. In certain cases, local regulations may also require some of the following information to be removed.

- Name and address of sponsor
- Protocol number
- Kit number
- Lot number
- Dosage form
- Quantity
- Storage conditions
- Expiration date
- Route of administration
- “To be Used as Instructed by the Clinical Study Documentation. For Clinical Trial Use Only.”

Each vial of IVT aflibercept will be labeled. The subject identification number will be recorded on each vial and the subject identification number and investigator name (if locally required) will be recorded on the kit boxes for all the treatment kits. The kit number will be recorded in the subject’s source documentation and entered into the eCRF.

### 7.5.3 Supply

The treatment kits will be shipped to the investigator at regular intervals or as needed during the study. Study drug will be shipped to the site using appropriate methods to maintain transport conditions within those recommended by its stability profile. The investigator, or an approved representative (e.g. pharmacist), will ensure that all received study drugs are stored in a secured area on site, under recommended storage conditions, and in accordance with applicable regulatory requirements.

### 7.5.4 Return

At the end of the study and following reconciliation and documentation by the site monitor, all used, partially used, and unused vials of IVT aflibercept will either be destroyed at the site or returned to a specified designee for disposal.

## 7.6 Treatment compliance

All injections will be given at the clinical site. Study personnel will monitor and document treatment compliance.

## 8. Non-study therapy

### 8.1 Prior and concomitant therapy – amended

For prohibited drugs and procedures prior to the study, see Section 6.

Subjects may not receive any treatment (approved or investigational) for macular edema secondary to CRVO in the study eye other than the assigned study treatment of IVT aflibercept until the Week 76 or early termination visit assessments are completed. This includes medications administered locally (e.g. by IVT, topical, juxtасcleral, subconjunctival, or periorbital routes) in the study eye or medications administered systemically with the intent of treating the study and/or the fellow eye, including systemic anti-VEGF therapy. In addition, macular laser photocoagulation is prohibited during the study (in the study eye). Intravitreal injections as well as other medications administered via other routes of administration (e.g. topical, juxtасcleral, subconjunctival, or periorbital routes) in the fellow eye are permitted.

All subjects may receive PRP rescue at any time during the study if deemed necessary by the investigator<sup>24</sup> and will continue to be assessed in this study.

Any other medications that are considered necessary for the subject's welfare, and that are not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator, with the exceptions noted above. Subjects are permitted to continue with ongoing medications needed to maintain stable disease management (e.g. hypertension, hyperlipidemia, and so forth) except for any medications specifically named in the exclusion criteria.

### 8.2 Post-study therapy

After the end of the study, subjects will be treated with either IVT aflibercept or other treatment according to their physician's decision. No additional therapy will be provided once subjects complete the trial.

## 9. Procedures and variables

### 9.1 Tabular Schedule of Evaluations

A tabular schedule of study evaluations and procedures is provided in [Table 9-1](#), Schedule of Evaluations and Study Procedures.

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<sup>24</sup> Removed conditions when subjects may receive PRP rescue, and added that subjects may receive PRP rescue per investigator discretion per Amendment 1, Modification 19 (see Section [15.1.1.19](#)).

**Table 9-1: Schedule of Evaluations and Study Procedures – amended**

Visit Description	Initiation Phase			T&E Phase				
	Screening <sup>a</sup>	Baseline <sup>a</sup>	Treatment Every 4 Weeks (2Q4) <sup>b</sup>	T&E Treatment Visits <sup>b</sup>	Interim <sup>b,c</sup>	Interim <sup>b,c</sup>	End of Study <sup>b</sup>	Early Termination
	Time Point	Visit 1 Day –21 to Baseline	Visit 2 (Day 1)	Visit 3 and following until stability achieved or Week 20 (± 7 days)	According to Individual T&E Schedule (± 7 days) <sup>d</sup>	Week 24 (± 7 days)	Week 52 (± 7 days)	Week 76 (± 7 days)
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographic data	X							
Medical/ophthalmic history	X							
Physical examination	X							
Pregnancy test <sup>e</sup>	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Refraction and BCVA (ETDRS chart starting at 4 m) <sup>f</sup>	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X
FA/FP <sup>g,h,i</sup>	X	X			X	X	X	X
AEs <sup>j</sup>	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy <sup>k</sup>	X	X	X	X	X	X	X	X
RAPD <sup>l</sup>		X			X	X	X	X
Slit lamp biomicroscopy	X	X	X	X	X	X	X	X
Gonioscopy <sup>m</sup>	X						X	X
IOP <sup>k</sup>	X	X	X	X	X	X	X	X
Full-field ERG <sup>h,i,n</sup>	(X)	X			X	X	X	X
Wide-field (angle) FA <sup>g,h,i,n</sup>	(X)	X			X	X	X	X
OCT angiography <sup>h,i,n</sup>	(X)	X			X	X	X	X

			Initiation Phase	T&E Phase				
Visit Description	Screening <sup>a</sup>	Baseline <sup>a</sup>	Treatment Every 4 Weeks (2Q4) <sup>b</sup>	T&E Treatment Visits <sup>b</sup>	Interim <sup>b,c</sup>	Interim <sup>b,c</sup>	End of Study <sup>b</sup>	Early Termination
Time Point	Visit 1 Day -21 to Baseline	Visit 2 (Day 1)	Visit 3 and following until stability achieved or Week 20 (± 7 days)	According to Individual T&E Schedule (± 7 days) <sup>d</sup>	Week 24 (± 7 days)	Week 52 (± 7 days)	Week 76 (± 7 days)	
Vital signs <sup>o</sup>	X	X	X	X	X	X	X	X
Administration of study treatment <sup>p</sup>		X	X	X	(X)	(X)	<sup>q</sup>	
Telephone safety check <sup>f</sup>		X	X	X	(X)	(X)	X	
Evaluation of posology, how disease activity is monitored, including monitoring frequency		X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; FP, fundus photography; IOP, intraocular pressure; OCT, optical coherence tomography; RAPD, relative afferent pupillary defect; SD-OCT; spectral domain optical coherence tomography T&E, Treat and Extend.

Note: Ocular assessments are to be conducted in both eyes unless otherwise indicated.

- a: The screening and baseline visits can be combined if eligibility criteria are met, all inclusion criteria are fulfilled, and none of the exclusion criteria apply. If screening and baseline occur on the same visit, pregnancy test results and reading center evaluations need to be available prior to treatment with study drug. The necessary procedures can be performed on separate days. However, slit lamp (anterior segment), IOP measurement, and indirect ophthalmoscopy are recommended to take place/be repeated on the same day as the IVT injection. There will be a 7-day window allowed for all procedures to be completed for the combined screening/baseline and the baseline visit.
- b: A ± 7-day window will be allowed for all post-baseline visits. The procedures required at each visit have to be completed within 7 days (i.e. split visits are allowed); however, all procedures have to be completed within the ± 7-day window. Slit lamp (anterior segment), IOP measurement, and indirect ophthalmoscopy are recommended to take place on the same day as the IVT injection.
- c: The visits at Weeks 24 and 52 do not pertain to the T&E posology; however, based on the subject's T&E schedule, the subject may receive IVT injection of study drug.
- d: Monitoring will be performed at each injection visit and at Weeks 24, 52, and 76. Starting at Week 8, the stability criteria will be evaluated as described in Section 7.1.2 and the frequency of injections may be adjusted (increased or decreased by 2-week intervals) to maintain stable visual and anatomic outcomes.
- e: Urine pregnancy test for women of child-bearing potential only. If positive, a serum pregnancy test for confirmation should be performed. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. After screening, a urine pregnancy test is mandatory for women of childbearing potential at every treatment visit (prior to injection) in all countries where it is required by local regulations. If required by local regulations, a pregnancy test should be performed for women of childbearing potential at the End of Study visit.
- f: Refraction and BCVA using the ETDRS chart are to be performed at each visit.
- g: If the investigator considers no significant change in indirect ophthalmoscopy, an additional FA/FP is not mandatory at the baseline visit. Traditional FA/FP examinations can be combined with wide-field examinations if possible. A separate fluorescein injection, especially, should be avoided.
- h: The treating investigator may perform these examinations at other times during the 76 weeks of the study based on his/her medical judgment and standard of care.
- i: Conduct in both eyes at screening/baseline and in the study eye only at the other visits indicated unless there are signs of vein occlusion in the fellow eye.

- j: Any AE occurring up to 30 days after the last injection of IVT aflibercept is to be documented regardless of the relationship to the study drug or the seriousness of the event, and reported in accordance with this protocol (see Section 9.6.1.3). A mandatory telephone safety contact with the investigator 30 days after the last administration of study medication is scheduled to ensure that the patient has not experienced any AEs.
- k: Conduct pre- and post-dose as applicable. If a subject receives a study injection, indirect ophthalmoscopy should be conducted post-dose and IOP should be assessed in the study eye 30 to 60 minutes after dosing.
- l: Conducted in both eyes (procedure for conducting RAPD testing is provided in the study manual). If the screening and baseline visits are combined, these assessments should be performed at the initial visit.
- m: Performed in the study eye only. Conducted at screening and at Week 76 and the early termination visit. May be repeated if needed as determined by the investigator.
- n: Conducted where feasible and available at selected sites. If the screening and baseline visits are combined, these assessments should be performed at the initial visit.
- o: Temperature, blood pressure, and heart rate.
- p: See Appendix 16.1 for an example study drug injection procedure. Note: Study drug will be administered according to the criteria and timing described in Section 7. If the investigator considers permanent resolution of macular edema, treatment may be discontinued, but monitoring should be continued with a follow-up visit at a minimum interval of 8 weeks and at all subsequent prescheduled visits (i.e. Weeks 24, 52, and 76).
- q: Subjects may receive treatment of their underlying disease at their physician's discretion at Week 76 after the end-of-study visit and the assessments for all variables are completed.
- r: A mandatory safety telephone call will be made within 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred.<sup>25</sup>

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<sup>25</sup> Details of changes to the Schedule of Evaluations and Study Procedures are displayed in Section 15.1.2 for modifications per Amendment 1, Modification 1 (see Section 15.1.1.1), Modification 2 (see Section 15.1.1.2), Modification 3 (Section 15.1.1.3), Modification 7 (see Section 15.1.1.7), Modification 8 (see Section 15.1.1.8), Modification 20 (see Section 15.1.1.20), Modification 21 (see Section 15.1.1.21), Modification 22 (see Section 15.1.1.22), Modification 23 (see Section 15.1.1.23), Modification 24 (see Section 15.1.1.24), Modification 25 (see Section 15.1.1.25), Modification 26 (see Section 15.1.1.26), Modification 27 (see Section 15.1.1.27), Modification 28 (see Section 15.1.1.28), Modification 29 (see Section 15.1.1.29), Modification 30 (see Section 15.1.1.30), and Modification 31 (see Section 15.1.1.31).

## 9.2 Visit descriptions – amended

The screening and baseline visits can be combined if eligibility criteria are met, all inclusion criteria are fulfilled, and none of the exclusion criteria apply. The necessary procedures can be performed on separate days.<sup>26</sup> There will be a 7-day window allowed for all procedures to be completed in such a combined visit.<sup>27</sup> If screening and baseline occur on the same visit, pregnancy test results and reading center evaluations need to be available prior to treatment with study drug. Furthermore, the additional examinations at baseline should be performed at the initial visit prior to treatment with study drug if the investigator intends to combine screening and baseline visit.<sup>28</sup>

### 9.2.1 Screening visit (Visit 1, Day –21 to baseline) – amended

- Obtain signed ICF
- Assess inclusion and exclusion criteria
- Obtain demographic data
- Prior and concomitant medications
- Obtain medical and ophthalmic history
- Physical examination
- Vital signs (temperature, blood pressure, and heart rate)
- Ocular assessments (to be conducted in both eyes unless otherwise indicated):
  - Refraction and BCVA using the ETDRS chart (to be performed at each visit)
  - SD-OCT
  - IOP
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Gonioscopy (study eye only)
  - FA/FP (the study manual will further specify the standards for FA/FP during the study)
- Pregnancy test (urine) for women of childbearing potential. If the result is positive, a serum pregnancy test will be done for confirmation. Postmenopausal women must be

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<sup>26</sup> Clarified that procedures may be performed on separate days if screening and baseline visits are combined per Amendment 1, Modification 20 (see Section 15.1.1.20).

<sup>27</sup> Added that for baseline and screening visits to be considered a combined visit, the assessments must take place within a 7-day window per Amendment 1, Modification 21 (see Section 15.1.1.21).

<sup>28</sup> Examinations required at baseline should be performed at the initial visit, prior to treatment with study drug, if the investigator intends to combine the screening and baseline visits per Amendment 1, Modification 28 (see Section 15.1.1.28).



amenorrhic for at least 12 months in order not to be considered of childbearing potential.

### 9.2.2 Baseline visit (Visit 2, Day 1) – amended

- Confirm inclusion criteria and exclusion criteria. This includes a negative pregnancy test for women of childbearing potential. Postmenopausal women must be amenorrhic for at least 12 months in order not to be considered of childbearing potential.
- A urine pregnancy test is mandatory prior to injection for women of childbearing potential in all countries where it is required by local regulations.<sup>29</sup>
- Confirm medical history of macular edema secondary to CRVO
- Prior and concomitant medications
- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)
- Ocular assessments (to be conducted in both eyes unless otherwise indicated):
  - Refraction and BCVA using the ETDRS chart (to be performed at each visit)
  - SD-OCT
  - IOP
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - RAPD test
  - FA/FP (the study manual will further specify the standards for FA/FP during the study). If the investigator considers no significant change in indirect ophthalmoscopy, an additional FA/FP is not mandatory at the baseline visit.<sup>30</sup> Traditional FA/FP examinations can be combined with wide-field examination if possible. A separate fluorescein injection, especially, should be avoided.<sup>31</sup>
  - Wide-field FA, at selected study sites (if screening and baseline visits are combined, assessment should be performed at the initial visit)<sup>32</sup>
  - OCT angiography, at selected study sites (if screening and baseline visits are combined, assessment should be performed at the initial visit)<sup>33</sup>

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<sup>29</sup> Added that pregnancy testing is mandatory for women of childbearing potential at every treatment visit prior to injection and at End of Study visit if required by local regulations per Amendment 1, Modification 24 (see Section 15.1.1.24).

<sup>30</sup> If there is no significant change in indirect ophthalmoscopy, an additional FA/FP at baseline is not required per Amendment 1, Modification 25 (see Section 15.1.1.25).

<sup>31</sup> When possible, FA/FP examinations can be combined with wide-field examination and separate fluorescein injection should be avoided per Amendment 1, Modification 26 (see Section 15.1.1.26).

<sup>32</sup> Added that assessment should be performed at the initial visit if screening and baseline visits are combined per Amendment 1, Modification 28 (see Section 15.1.1.28).

- Full-field ERG, at selected study sites (if screening and baseline visits are combined, assessment should be performed at the initial visit)<sup>34</sup>
- IVT injection of study drug (see Appendix 16.1 for an example study drug injection procedure), followed by a 30- to 60-minute observation period
  - Measure IOP again in the study eye 30 to 60 minutes following IVT injection
  - Indirect ophthalmoscopy (post-dose)
  - Mandatory safety telephone call within 3 days<sup>35</sup> after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

### 9.2.3 Initiation phase (2Q4 treatment intervals $\pm$ 7 days) - amended

- Prior and concomitant medications
- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)
- A urine pregnancy test is mandatory prior to injection for women of childbearing potential in all countries where it is required by local regulations<sup>36</sup>
- Ocular assessments (to be conducted in both eyes unless otherwise indicated):
  - Refraction and BCVA using the ETDRS chart (to be performed at each visit)
  - Slit lamp biomicroscopy
  - SD-OCT
  - IOP
  - Indirect ophthalmoscopy
  - IVT injection of study drug (see Appendix 16.1 for an example study drug injection procedure), followed by a 30- to 60-minute observation period
  - Measure IOP again in the study eye 30 to 60 minutes following IVT injection
  - Indirect ophthalmoscopy (post-dose)
  - Mandatory safety telephone call within 3 days<sup>37</sup> after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

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<sup>33</sup> Added that assessment should be performed at the initial visit if screening and baseline visits are combined per Amendment 1, Modification 28 (see Section 15.1.1.28).

<sup>34</sup> Added that assessment should be performed at the initial visit if screening and baseline visits are combined per Amendment 1, Modification 28 (see Section 15.1.1.28).

<sup>35</sup> Schedule for safety follow-up telephone calls changed from 3 days after treatment to within 3 days per Amendment 1, Modification 30 (see Section 15.1.1.30).

<sup>36</sup> Added mandatory pregnancy testing for women of childbearing potential at every treatment visit prior to injection and at End of Study visit if required by local regulations per Amendment 1, Modification 24 (see Section 15.1.1.24).

- IVT injection of study drug (see Appendix 16.1 for an example study drug injection procedure), followed by a 30- to 60-minute observation period

## 9.2.4 Treat and Extend phase

### 9.2.4.1 Treat and Extend visits – amended

Treat and Extend visits are scheduled according to an individual subject's T&E schedule ( $\pm 7$  days).<sup>38</sup>

- Prior and concomitant medications
- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)
- A urine pregnancy test is mandatory prior to injection for women of childbearing potential in all countries where it is required by local regulations<sup>39</sup>
- Ocular assessments (to be conducted in both eyes unless otherwise indicated):
  - Refraction and BCVA using the ETDRS chart (to be performed at each visit)
  - SD-OCT
  - IOP
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
- IVT injection of study drug (see Appendix 16.1 for an example study drug injection procedure), followed by a 30- to 60-minute observation period
  - Measure IOP again in the study eye 30 to 60 minutes following IVT injection
  - Indirect ophthalmoscopy (post-dose)
  - Mandatory safety telephone call within 3 days<sup>40</sup> after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

### 9.2.4.2 Week 24 ( $\pm 7$ days) interim visit – amended

- Prior and concomitant medications
- Vital signs (temperature, blood pressure, and heart rate)

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<sup>37</sup> Schedule for safety follow-up telephone calls changed from 3 days after treatment to within 3 days per Amendment 1, Modification 30 (see Section 15.1.1.30).

<sup>38</sup> Added a  $\pm 7$ -day window to Treat and Extend visits to clarify window for all post-baseline visits per Amendment 1, Modification 7 (see Section 15.1.1.7).

<sup>39</sup> Added mandatory pregnancy testing for women of childbearing potential at every treatment visit prior to injection and at End of Study visit if required by local regulations Amendment 1, Modification 24 (see Section 15.1.1.24).

<sup>40</sup> Schedule for safety follow-up telephone calls changed from 3 days after treatment to within 3 days per Amendment 1, Modification 30 (see Section 15.1.1.30).

- AEs (pre- and post-dose)
- A urine pregnancy test is mandatory prior to injection for women of childbearing potential in all countries where it is required by local regulations<sup>41</sup>
- Ocular assessments (to be conducted in both eyes unless otherwise indicated)
  - Refraction and BCVA using the ETDRS chart (to be performed at each visit)
  - SD-OCT
  - IOP
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - RAPD test
  - FA/FP (study eye only unless there are signs of vein occlusion in the fellow eye; the study manual will further specify the standards for FA/FP during the study)
  - Wide-field FA (study eye only unless there are signs of vein occlusion in the fellow eye) at selected study sites
  - OCT angiography (study eye only unless there are signs of vein occlusion in the fellow eye) at selected study sites
  - Full-field ERG (study eye only unless there are signs of vein occlusion in the fellow eye) at selected study sites
- The Week 24 visit does not pertain<sup>42</sup> to the T&E posology. The posology should follow the retreatment criteria and not be adjusted to coincide with the Week 24 monitoring visit. However, if the subject meets the criteria outlined in Section 7.1.3 (T&E phase treatment criteria), the subject may receive IVT injection of study drug (see Appendix 16.1 for an example study drug injection procedure), followed by a 30- to 60-minute observation period.
  - Measure IOP again in the study eye 30 to 60 minutes following IVT injection
  - Indirect ophthalmoscopy (post-dose)
  - Mandatory safety telephone call within 3 days<sup>43</sup> after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

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<sup>41</sup> Added mandatory pregnancy testing for women of childbearing potential at every treatment visit prior to injection and at End of Study visit if required by local regulations Amendment 1, Modification 24 (see Section 15.1.1.24).

<sup>42</sup> Wording changed from “is not a visit pertaining” to “does not pertain” in reference to T&E posology per Amendment 1, Modification 31 (see Section 15.1.1.31).

<sup>43</sup> Revised schedule for safety follow-up telephone calls from 3 days after treatment to within 3 days per Amendment 1, Modification 30 (see Section 15.1.1.30).



### 9.2.4.3 Week 52 ( $\pm$ 7 days) interim visit – amended

- Prior and concomitant medications
- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)
- A urine pregnancy test is mandatory prior to injection for women of childbearing potential in all countries where it is required by local regulations<sup>44</sup>
- Ocular assessments (to be conducted in both eyes unless otherwise indicated)
  - Refraction and BCVA using the ETDRS chart (to be performed at each visit)
  - SD-OCT
  - IOP
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - RAPD test
  - FA/FP (study eye only unless there are signs of vein occlusion in the fellow eye, the study manual will further specify the standards for FA/FP during the study)
  - Wide-field FA (study eye only unless there are signs of vein occlusion in the fellow eye) at selected study sites
  - OCT angiography (study eye only unless there are signs of vein occlusion in the fellow eye) at selected study sites, evaluation of posology, how disease activity is monitored, including monitoring frequency
  - Full-field ERG (study eye only unless there are signs of vein occlusion in the fellow eye) at selected study sites
- The Week 52 visit does not pertain to the T&E posology. The posology should follow the retreatment criteria and not be adjusted to coincide with the Week 52 monitoring visit. However, if the subject meets the criteria outlined in Section 7.1.3 (T&E phase treatment criteria), the subject may receive IVT injection of study drug (see Appendix 16.1 for an example study drug injection procedure), followed by a 30- to 60-minute observation period.
  - Measure IOP again in the study eye 30 to 60 minutes following IVT injection
  - Indirect ophthalmoscopy (post-dose)

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<sup>44</sup> Added pregnancy testing is mandatory for women of childbearing potential at every treatment visit prior to injection and at End of Study visit if required by local regulations per Amendment 1, Modification 24 (see Section 15.1.1.24).

- Mandatory safety telephone call within 3 days<sup>45</sup> after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

#### 9.2.4.4 Week 76 ( $\pm$ 7 days) final study visit – amended

- Prior and concomitant medications
- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)
- Ocular assessments (to be conducted in both eyes unless otherwise indicated):
  - Refraction and BCVA using the ETDRS chart (to be performed at each visit)
  - SD-OCT
  - IOP
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Gonioscopy (study eye only)
  - RAPD test
  - FA/FP (study eye only unless there are signs of vein occlusion in the fellow eye, the study manual will further specify the standards for FA/FP during the study)
  - Wide-field FA (study eye only unless there are signs of vein occlusion in the fellow eye) at selected study sites
  - OCT angiography (study eye only unless there are signs of vein occlusion in the fellow eye) at selected study sites
  - Full-field ERG (study eye only unless there are signs of vein occlusion in the fellow eye) at selected study sites
- The Week 76 visit does not pertain to the T&E posology.<sup>46</sup> However, if treatment of the patient's underlying disease is needed on that day, it will not be part of the study and no study drug can be injected. Treatment is up to the discretion/decision of the patient's physician. Such treatment should only occur after all study relevant assessments have been performed.
- Any AE occurring up to 30 days after the last injection of study drug is to be documented regardless of the relationship to the study drug or the seriousness of the event, and reported in accordance with this protocol. (see Section 9.6.1.3). A mandatory telephone safety contact with the investigator 30 days after the last

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<sup>45</sup>Revised schedule for safety follow-up telephone calls from 3 days after treatment to within 3 days per Amendment 1, Modification 30 (see Section 15.1.1.30).

<sup>46</sup>Wording changed from "is not a visit pertaining" to "does not pertain" in reference to T&E posology per Amendment 1, Modification 31 (see Section 15.1.1.31).

administration of study medication is scheduled to ensure that the patient has not experienced any AEs.<sup>47</sup>

### 9.2.5 Early termination visit – amended

- <sup>48</sup>Prior and concomitant medications
- Vital signs (temperature, blood pressure, and heart rate)
- AEs
- Ocular assessments (to be conducted in both eyes unless otherwise indicated):
  - Refraction and BCVA using the ETDRS chart (to be performed at each visit)
  - SD-OCT
  - IOP
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Gonioscopy (study eye only)
  - RAPD test
  - FA/FP (study eye only unless there are signs of vein occlusion in the fellow eye, the study manual will further specify the standards for FA/FP during the study)
  - Wide-field FA (study eye only unless there are signs of vein occlusion in the fellow eye) at selected study sites.
  - OCT angiography (study eye only unless there are signs of vein occlusion in the fellow eye) at selected study sites
  - Full-field ERG (study eye only unless there are signs of vein occlusion in the fellow eye) at selected study sites
- Any AE occurring up to 30 days after the last injection of IVT aflibercept is to be documented regardless of the relationship to the study drug or the seriousness of the event, and reported in accordance with this protocol (see Section 9.6.1.3). A mandatory telephone safety contact with the investigator 30 days after the last administration of study medication is scheduled to ensure that the patient has not experienced any AEs.<sup>49</sup>

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<sup>47</sup> Reworded for clarity that telephone contact is a safety telephone contact with the investigator 30 days after last dose of study drug to ensure patient has not experienced any AEs per Amendment 1, Modification 27 (see Section 15.1.1.27).

<sup>48</sup> Removed sentence describing monitoring interval if subject is withdrawn from the study per Amendment 1, Modification 32 (see Section 15.1.1.32).

<sup>49</sup> Reworded for clarity that telephone contact is a safety telephone contact with the investigator 30 days after last dose of study drug to ensure patient has not experienced any AEs per Amendment 1, Modification 27 (see Section 15.1.1.27).

## 9.3 Population characteristics

### 9.3.1 Demographic

Subjects will be recruited from men and women  $\geq 18$  years of age. The following demographic parameters will be recorded:

- Sex
- Year of birth
- Weight
- Height
- Race/ethnicity

### 9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases, or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- A complete medical and ophthalmic history will be obtained
- Start date before signing of the informed consent
- Considered relevant for the subject's study eligibility

Detailed instructions on the differentiation between medical history and AEs can be found in Section [9.6.1.1](#).

### 9.3.3 Other baseline characteristics

Subjects participating in this study will have a diagnosis of macular edema secondary to CRVO. Visual function of the study eye at the initiation of IVT aflibercept treatment must be an ETDRS letter score of 73 to 24 letters (Snellen equivalent of 20/40 to 20/320).

## 9.4 Efficacy

### 9.4.1 Primary efficacy variables

- The proportion of subjects who gain  $\geq 15$  letters in BCVA on the ETDRS chart compared with baseline at Week 76
- The proportion of subjects with a mean treatment interval between injections of  $\geq 8$  weeks from the last actual visit of the initiation phase to Week 76

### 9.4.2 Secondary efficacy variables - amended

- The change in BCVA as measured by the ETDRS letter score from baseline to Weeks 24, 52, and 76
- The change in CRT from baseline to Weeks 24, 52, and 76
- The number of injections from baseline to Week 76
- The mean treatment interval between injections from baseline to Week 76





- The proportion of subjects who gain  $\geq 15$  letters in BCVA on the ETDRS chart compared with baseline at Weeks 24 and 52
- The change in retinal perfusion (FA/FP) status from screening/baseline<sup>50</sup> to Weeks 24, 52, and 76
- The proportion of subjects with absence of fluid at Weeks 24, 52, and 76

#### 9.4.3 Exploratory efficacy variables - amended

- Perfusion status of the retina assessed by wide-field FA at screening/baseline,<sup>51</sup> Weeks 24, 52, and 76
- OCT angiography measures for assessing perfusion status of the retina and examination of morphological changes related to disease progression in CRVO at baseline, Weeks 24, 52, and 76
- Full-field ERG assessments at baseline, Weeks 24, 52, and 76
- Status of RAPD at baseline, Weeks 24, 52, and 76

Table 9-2 shows the schedule of efficacy variable assessments.

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<sup>50</sup> Clarified that assessment of secondary variable of change in retinal perfusion status will include screening/baseline combined visit per Amendment 1, Modification 3 (see Section 15.1.1.3).

<sup>51</sup> Clarified that assessment of exploratory variable of perfusion status of the retina by wide-field FA will include screening/baseline combined visit. per Amendment 1, Modification 9 (see Section 15.1.1.9).

**Table 9-2: Schedule of Efficacy Variable Assessments**

	WEEK 24	WEEK 52	WEEK 76
<b>PRIMARY EFFICACY VARIABLES</b>			
The proportion of subjects who gain $\geq 15$ letters in BCVA on the ETDRS chart compared with baseline at Week 76			X
The proportion of subjects with a mean treatment interval between injections of $\geq 8$ weeks from the last actual visit of the initiation phase to Week 76			X
<b>SECONDARY EFFICACY VARIABLES</b>			
The change in BCVA as measured by the ETDRS letter score from baseline to Weeks 24, 52, and 76	X	X	X
The change in CRT from baseline to Weeks 24, 52, and 76	X	X	X
The number of injections from baseline to Week 76			X
The mean treatment interval between injections from baseline to Week 76			X
The proportion of subjects who gain $\geq 15$ letters in BCVA on the ETDRS chart compared with baseline at Weeks 24 and 52	X	X	
The change in retinal perfusion (FA/FP) status from screening/baseline <sup>52</sup> to Weeks 24, 52, and 76	X	X	X
The proportion of subjects with absence of fluid at Weeks 24, 52, and 76	X	X	X
<b>EXPLORATORY EFFICACY VARIABLES<sup>a</sup></b>			
Perfusion status of the retina assessed by wide-field FA at screening/baseline <sup>53</sup> Weeks 24, 52, and 76	X	X	X
OCT angiography measures for assessing perfusion status of the retina and examination of morphological changes related to disease progression in CRVO at baseline, Weeks 24, 52, and 76	X	X	X
Full-field ERG assessments at baseline, Weeks 24, 52, and 76	X	X	X
Status of RAPD at baseline, Weeks 24, 52, and 76	X	X	X

Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; CRVO, central retinal vein occlusion; ERG, electroretinogram; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; FP, fundus photography; OCT, optical coherence tomography; RAPD, relative afferent pupillary defect.

a: At selected sites where instrumentation and technical competence are available. If screening and baseline visits are combined, these assessments should be performed at the initial visit.<sup>54</sup>

<sup>52</sup> Clarified that assessment of secondary variable of change in retinal perfusion status will include screening/baseline combined visit per Amendment 1, Modification 3 (see Section 15.1.1.3).

<sup>53</sup> Clarified that exploratory variable of perfusion status will be assessed by wide-field FA including at screening/baseline combined visit per Amendment 1, Modification 9 (see Section 15.1.1.9).

<sup>54</sup> Added that assessments should be performed at the initial visit if screening and baseline visits are combined per Amendment 1, Modification 28 (see Section 15.1.1.28).

#### **9.4.4 Efficacy procedures**

Assessments of efficacy will include BCVA, SD-OCT, and FA/FP. At selected sites where instrumentation and technical competence is available, assessments will also include wide-field FA, OCT angiography, and full-field ERG.

Study manual refers to all manuals used in the study including central reading evaluation and BCVA assessment.

##### **9.4.4.1 Best-corrected visual acuity**

Visual function of the study eye and the fellow eye will be assessed at each study visit using the ETDRS visual acuity chart starting at 4 meters. Visual acuity examiners must be certified to ensure consistent measurement of BCVA. A detailed protocol for conducting visual acuity testing and refraction is provided in the study manual.

##### **9.4.4.2 Spectral domain optical coherence tomography**

Retinal characteristics such as CRT will be evaluated by SD-OCT in both eyes at every study visit. Images of the study eye will be captured and assessed by study-site personnel.

Initially, the SD-OCT images taken at the study site of up to 2 volunteers per site may be assessed by the central reading site to certify the site for central reading. During the study, all SD-OCT images will be reviewed and assessed by readers at the central reading center.

Additional details regarding the SD-OCT procedure will be provided in the study manual.

All SD-OCT assessments will be archived as part of the subject's source documentation.

##### **9.4.4.3 Fluorescein angiography and fundus photography – amended**

The anatomical state of the retinal vasculature of the study eye will be evaluated by funduscopic examination, FP and FA. Fundus photography and FA obtained at the screening visit will be reviewed by the central reading center to confirm eligibility. During the study, all additional scheduled FA and FP images will be reviewed and assessed by readers at the central reading center.

To evaluate perfusion status, FA and FP will be performed on subjects according to the schedule as described in Section 9.2. The area of posterior retinal capillary non-perfusion will be measured on FAs by certified graders at the central reading center.

In addition to the required FA/FP evaluations at screening/baseline, Weeks 24, 52, and 76, and the early termination visit, the investigator may perform additional FA/FP evaluations at other times during the study based on his/her medical judgment and standard of care. At screening/baseline, FA/FP will be assessed in both eyes. Unless there are signs of vein occlusion in the fellow eye, FA and FP will not be assessed in the fellow eye at Weeks 24, 52, 76, or at the early termination visit. As such images would be obtained outside the framework of this protocol, they should not be routinely forwarded by the investigator/study site to the central reading center. Traditional FA/FP examinations can be combined with wide-field examination if possible. A separate fluorescein injection, especially, should be

avoided.<sup>55</sup> Additional details regarding the FA and FP procedure will be provided in the study manual.

All FA and FP images will be archived as part of the subject's source documentation.

#### **9.4.4.4 Wide-field fluorescein angiography – amended**

Angiographic images will be captured for a subpopulation at selected sites using instrumentation with so-called “wide-field” or “ultra-wide-field” capture systems, which can increase the viewable retinal surface from 30° up to 50° to 200° for visualization of the perifoveal area. A shortcoming of most existing studies is the lack of visualization of the retinal periphery, which is limited by the standard 30° or 60° images of traditional FA. Even with composite images, which can provide a 75° view of the retina, the majority of the retinal periphery is still not visualized. Thus, limited information is available about the role that this region may play in retinal ischemia, macular edema, and vision loss in eyes with RVO. Wide-field FA provides a new method to visualize more than 100° of the retina using a non-contact lens-based system to assess peripheral perfusion status in RVO.

Wide-field FA of both eyes will be performed at baseline (or initial visit at combined screening/baseline),<sup>56</sup> and of only the study eye at Weeks 24, 52, and 76, and the early termination visit (and in the fellow eye if there are signs of vein occlusion). Specific registration procedures will be employed to reproduce the location for imaging longitudinally. The protocol for imaging and analysis procedures will be described in the study manual. Peripheral perfusion status will be reported in terms of clock position (e.g. 12 o'clock).

All images will be assessed at the central reading center. All wide-field FA images will be archived as part of the subject's source documentation.

#### **9.4.4.5 Optical coherence tomography angiography – amended**

Optical coherence tomography angiography will be assessed for a subpopulation at selected sites using OCT angiography.

Optical coherence tomography angiography assists in the visualization of the ocular vasculature and quantification of blood flow at the posterior pole of the eye. The OCT angiography technique offers 2 major advantages over standard techniques such as FA: no dye is required and depth resolution is provided for visualization of retinal capillaries. Optical coherence tomography angiography has the potential to improve our abilities to diagnose and monitor ocular vascular diseases.

Optical coherence tomography angiography images of both eyes will be captured at baseline (or initial visit at combined screening/baseline)<sup>57</sup> and of only the study eye at Weeks 24, 52, and 76, and the early termination visit (and in the fellow eye if there are signs of vein

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<sup>55</sup> When possible, FA/FP examinations can be combined with wide-field examination and separate fluorescein injection should be avoided per Amendment 1, Modification 26 (see Section 15.1.1.26).

<sup>56</sup> Added that assessment should be performed at initial visit if screening and baseline visits are combined per Amendment 1, Modification 28 (see Section 15.1.1.28).

<sup>57</sup> Added that assessment should be performed at initial visit if screening and baseline visits are combined per Amendment 1, Modification 28 (see Section 15.1.1.28).

occlusion). Additional details regarding the imaging measures will be provided in the study manual.

All OCT angiography images will be assessed at the central reading center.

All OCT angiography images will be archived as part of the subject's source documentation.

#### **9.4.4.6 Full-field electroretinography – amended**

Electroretinograms will be taken for a subpopulation at selected sites using full-field ERG.

Electroretinography is a non-invasive examination that was introduced in 1945 by Karpe (20) as a possible prognostic marker in patients with macular edema secondary to CRVO. Since then, others have demonstrated that different parameters of the ERG can be helpful in distinguishing between ischemic and non-ischemic forms of CRVO. Hayreh confirmed that full-field ERG specifically decreased B-wave amplitude coupled with the so-called RAPD test, differentiated ischemic from non-ischemic CRVO in subjects with a 97% sensitivity, and that this combined testing constituted the most reliable method for identifying ischemic subjects (21).

Full-field ERG is a widely used electrophysiologic test of retinal function. The International Society for Clinical Electrophysiology of Vision (ISCEV) established standardized basic clinical ERG protocols so that comparable ERGs could be recorded across different sites. The ISCEV standard for full-field clinical ERG (2015 update) will serve as a methodological basis for this study (22). Electroretinography may be more sensitive to detect ischemia than angiography, especially in the early stages when retinal hemorrhages may limit angiographic interpretation.

Full-field ERGs will be performed in both eyes at baseline (or initial visit at combined screening/baseline)<sup>58</sup> and only in the study eye at Weeks 24, 52, and 76, and the early termination visit (and in the fellow eye if there are signs of vein occlusion). Additional details regarding the full-field ERG procedure will be provided in the study manual.

Electroretinogram images will be assessed at the site by the investigator.

All full-field ERG images will be archived as part of the subject's source documentation.

### **9.5 Pharmacokinetics/pharmacodynamics**

Not applicable.

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<sup>58</sup> Added that assessment should be performed at initial visit if screening and baseline visits are combined per Amendment 1, Modification 28 (see Section 15.1.1.28).



## 9.6 Safety

### 9.6.1 Adverse events

#### 9.6.1.1 Definitions

##### Definition of adverse event

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom, or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term “condition” may include abnormal physical examination findings, symptoms, diseases, laboratory findings, or other abnormal findings.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as AEs. This includes intercurrent illnesses.

##### Definition of serious adverse event

A serious AE (SAE) is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a-f):

- a. Results in death
- b. Is life-threatening

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

- c. Requires inpatient hospitalization or prolongation of existing hospitalization

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least 1 of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours

- The admission is pre-planned (i.e. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)
- The admission is not associated with an AE (e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of ‘medically important’ and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability/incapacity

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

e. Is a congenital anomaly/birth defect

f. Is another serious or important medical event as judged by the investigator

### 9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

#### 9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

#### 9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild
- Moderate
- Severe

#### 9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the eCRF.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”



An assessment of “no” would include:

- The existence of a highly likely alternative explanation (e.g. mechanical bleeding at surgical site),  
or
- Non-plausibility (e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration).

An assessment of “yes” indicates that that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: the event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Subject’s response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical.
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study treatment: the pharmacokinetic properties (absorption, distribution, metabolism, and excretion) of the study treatment, coupled with the individual subject’s pharmacodynamics should be considered.
- The assessment is not possible.

In this study, AEs will be assessed as related/not related to the study drug, IVT injection, and other protocol-specified procedures. The causal relationship will be recorded using the following terms:

#### **Evaluation of relationship to the study drug**

- Not related: AEs that were clearly and incontrovertibly due to causes other than the study drug (e.g. disease, environment), or were felt with a reasonable degree of certainty to be unrelated to the study drug.



- Related: AEs for which a connection with the study drug could not be ruled out with certainty, or were felt with a reasonable degree of certainty to be related to the study drug, or were incontrovertibly related to the study drug.

A possible example of a drug-related AE would be a hypersensitivity reaction.

#### **Evaluation of relationship to the injection procedure**

- Not related: AEs that were clearly and incontrovertibly due to causes other than the IVT injection procedure (e.g. disease, environment) or were felt with a reasonable degree of certainty to be unrelated to the IVT injection procedure.
- Related: AEs for which a connection with the IVT injection procedure could not be ruled out with certainty, or which were felt with a reasonable degree of certainty to be related to the IVT injection procedure, or which were incontrovertibly related to the IVT injection procedure.

A possible example of an injection-related AE would be eye pain at the site of the injection.

#### **Evaluation of relationship to study conduct**

- Not related: AEs that were clearly and incontrovertibly due to causes other than a protocol-specified procedure (e.g. disease, environment), or were felt with a reasonable degree of certainty to be unrelated to a protocol-specified procedure other than the IVT injection.
- Related: AEs for which a connection to a protocol-specified procedure other than the IVT injection could not be ruled out with certainty, or which were felt with a reasonable degree of certainty to be related to a protocol-specified procedure other than the IVT injection, or which were incontrovertibly related to a protocol-specified procedure other than the IVT injection.

A possible example of a procedure-related AE would be bruising at the site of a blood draw.

#### **9.6.1.2.4 Action taken with study treatment**

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Dose not changed
- Not applicable
- Unknown

#### **9.6.1.2.5 Other specific treatment(s) of adverse events**

- None
- Remedial drug therapy
- Other

### 9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

### 9.6.1.3 Assessments and documentation of adverse events

Attention is to be paid to the occurrence of AEs at all stages of the examination. Thus, the subject should be closely observed by the investigator. In case of ongoing drug- or injection-related AEs and medically relevant AEs at the end of the study, the investigator should monitor the subject and document the outcome on the subject's source documents.

The investigator must record on the respective eCRF pages all AEs occurring in the period between the signing of the informed consent and the end of the follow-up phase; after the end of the follow-up phase, there is no requirement to actively collect AEs, including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

“Death” should not be recorded as an AE on the AE page. Instead, “death” is the outcome of underlying AE(s).

For all AEs and SAEs, the sponsor has to carry out a separate assessment for expectedness, seriousness, and causal relationship to study drug.

Any AE occurring up to 30 days after the last injection of IVT aflibercept is to be documented regardless of the relationship to the study drug or the seriousness of the event, and reported in accordance with this protocol (i.e. not as a spontaneous report). For any drug-related AE occurring after 30 days after the last application of IVT aflibercept, the standard procedures that are in place for spontaneous reporting will be followed. If a subject prematurely withdraws from the study, AEs should be recorded until withdrawal or 30 days after the last dose of study drug, whichever is later.

### 9.6.1.4 Reporting of serious adverse events

The definition of an SAE is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

#### Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

All SAEs occurring during the observation period defined in Section 9.6.1.3 must immediately (within 24 hours of the investigator's awareness) be reported to the recipient detailed in the manual. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient. For this, an AE page in the eCRF as well as the complementary pages provided in the Investigator File must be completed for each SAE.

Serious AEs will be collected up until 30 days after the last dose of study drug or the early termination visit, whichever is later.

Serious AEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

#### **Notification of the Independent Ethics Committees/Institutional Review Boards**

Notification of the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) about all relevant events (e.g. SAEs, suspected unexpected serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

#### **Notification of the authorities**

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

#### **Sponsor's notification of the investigational site**

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

#### **9.6.1.5 Expected adverse events**

For this study, the applicable reference document is the most current version of the Company Core Data Sheet.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document (Company Core Data Sheet) and according to all local regulations.

#### **9.6.2 Pregnancies**

The investigator must report to the sponsor any pregnancy occurring in a study subject during her participation in this study, although a pregnancy per se is not considered an SAE. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

For a pregnancy in the partner of a male study subject, all efforts will be made to obtain similar information on course and outcome, subject to the partner's consent.

The child's health should be followed up for a post-natal period of not less than 3 months.

### **9.6.3 Further safety**

#### **9.6.3.1 Pregnancy test – amended**

All women of child-bearing potential will have a urine pregnancy test at screening. If the result of a urine pregnancy test is positive, a serum pregnancy test to confirm results will be done at a local laboratory. After screening, a urine pregnancy test for women of childbearing potential is mandatory at every treatment visit (prior to injection) in all countries where it is required by local regulations. If required by local regulations, a pregnancy test should be performed for women of childbearing potential at the End of Study visit.<sup>59</sup>

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

#### **9.6.3.2 Physical examination**

At screening (Visit 1), a complete physical examination will be performed. Abnormal physical examination findings are recorded either as medical history or as AEs (see Section 9.6.1.1).

#### **9.6.3.3 Vital signs (temperature, blood pressure, and heart rate)**

Temperature, blood pressure, and heart rate will be measured at all study visits (and early termination if applicable). Temperature and blood pressure should be taken in a consistent manner.

#### **9.6.3.4 Ocular safety**

Assessments of ocular safety will include IOP, indirect ophthalmoscopy, and slit lamp biomicroscopy. Relative afferent pupillary defect will also be assessed.

##### **9.6.3.4.1 Intraocular pressure**

Intraocular pressure will be measured in both eyes at all visits. At visits where the study drug is administered, IOP will be measured pre-dose in both eyes and again 30 to 60 minutes post-dose in the study eye. Any case of new-onset clinically significant increase in IOP that does not respond to treatment (not including the transient pressure rise observed immediately after IVT injection) must be recorded by the investigator as an AE.

Intraocular pressure is to be measured using applanation tonometry (Goldmann or Tono-Pen). The same method of IOP measurement must be used in each subject throughout the study. Non-contact tonometry may be used, but re-examination with applanation tonometry is recommended in cases where pathological IOP (> 22 mm Hg) is detected.

For the measurement of IOP, a local anesthetic combined with fluorescein must be topically applied to the eye being tested (e.g. 1 drop of oxybuprocain plus fluorescein).

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<sup>59</sup> Added that pregnancy testing is mandatory for women of childbearing potential at every treatment visit prior to injection and at End of Study visit if required by local regulations per Amendment 1, Modification 24 (see Section 15.1.1.24).

#### 9.6.3.4.2 Indirect ophthalmoscopy

Indirect ophthalmoscopy is to be obtained in a standard manner (i.e. usually using a head-mounted light source and a 20-diopter lens).

#### 9.6.3.4.3 Slit lamp biomicroscopy

The slit lamp examination is to be performed in both the study eye and the fellow eye irrespective of whether the fellow eye has macular edema secondary to CRVO. If the fellow eye is not diagnosed with macular edema secondary to CRVO, it will be followed to determine whether macular edema secondary to CRVO develops.

- Anterior segment assessment: The examination of the anterior segment is to be performed only with the slit lamp without any additive drugs or lenses.
- Posterior segment assessment: The posterior segment should be examined with the slit lamp and the appropriate lens. For this examination, the pupil of the eye must be dilated (mydriasis) with 2 to 3 drops of phenylephrin-tropicamide (or any other mydriatic) applied topically to the eye.

#### 9.6.3.4.4 Gonioscopy

Subjects will be evaluated for the development of neovascularization and/or scarring of the iridocorneal angle by gonioscopy in conjunction with slit lamp biomicroscopy. Subjects with neovascularization of the iris or neovascularization of the anterior chamber angle at screening should be excluded from the study.

The evaluation will be conducted at screening and at Week 76 and the early termination visit, and may be repeated if needed as determined by the investigator. Gonioscopy will be performed in the study eye only.<sup>60</sup>

#### 9.6.3.4.5 Relative afferent pupillary defect assessment

Testing for RAPD will be conducted at baseline, Weeks 24, 52, and 76, and the early termination visit. Testing will be conducted in both eyes.<sup>61</sup> A detailed protocol for conducting RAPD testing is provided in the study manual.

### 9.7 Appropriateness of procedures and measurements

All efficacy and safety variables and the methods by which they are assessed are standard variables and methods in clinical studies and in ophthalmic practice. They are widely used and generally recognized as reliable, accurate, and relevant.

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<sup>60</sup> Removed wording that gonioscopy is performed after OCT and before FA/FP per Amendment 1, Modification 29 (see Section 15.1.1.29).

<sup>61</sup> Removed citation to reference Thompson HS, et al per Amendment 1, Modification 33 (see Section 15.1.1.33).

## 10. Statistical methods and determination of sample size

### 10.1 General considerations

Further details on statistical evaluation, including format and content of tables, will be detailed in the statistical analysis plan (SAP). The SAP will be finalized before study database lock.

All variables will be analyzed descriptively with appropriate statistical methods: continuous variables by sample statistics (i.e. mean, standard deviation, median, quartiles, minimum, and maximum) and categorical variables by frequency tables (absolute and relative frequencies). Statistical analyses will be performed using Statistical Analysis System (SAS) version 9.2 or higher.

Sample size and disposition information by analysis time point will be displayed in a frequency table.

### 10.2 Analysis sets

Populations for analysis will be defined as follows:

The Full Analysis Set will include all enrolled subjects who received any study drug, have a baseline BCVA assessment, and have at least 1 post-baseline BCVA assessment. With regard to the efficacy evaluation of this study, the Full Analysis Set is considered the primary analysis.

The Per-protocol Set will include all enrolled subjects who receive any study drug, have a BCVA assessment at study baseline, have at least 1 BCVA assessment at Week 24 or later, and do not have a major protocol deviation.

The Safety Analysis Set will include all subjects who receive any study drug under this protocol.

A subgroup analysis of the primary endpoint will be performed for each country contributing at least 5 patients to the Full Analysis Set.

### 10.3 Variables and planned statistical analyses

#### 10.3.1 Variables – amended

A complete list of efficacy variables is provided in Section 9.4. Safety variables are detailed in Section 9.6.

A  $\pm$  7-day window will be allowed for all post-baseline visits.<sup>62</sup>

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<sup>62</sup> Revised wording to clarify that a  $\pm$  7-day window will be allowed for all post-baseline visits per Amendment 1, Modification 7 (see Section 15.1.1.7).

## 10.3.2 Statistical and analytical plans

### 10.3.2.1 Demography and baseline characteristics

Demographic variables and baseline characteristics will be summarized for all 3 analysis populations, depending on the type of data as described in Section 10.1. Medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA) codes and prior and concomitant medications by Anatomical Therapeutic Chemical codes (World Health Organization Drug Dictionary).

#### 10.3.2.2 Efficacy analyses

##### 10.3.2.2.1 Primary efficacy analyses

The primary efficacy variable analysis will be conducted on the Full Analysis Set and Per-protocol Set as defined in Section 10.2.

The co-primary efficacy variables are as follows:

- The proportion of subjects who gain  $\geq 15$  letters in BCVA on the ETDRS chart compared with baseline at Week 76
- The proportion of subjects with a mean treatment interval between injections of  $\geq 8$  weeks from the last actual visit of the initiation phase to Week 76

##### **Definition: Gain $\geq 15$ letters in BCVA at Week 76 compared with baseline**

Subjects will be considered to be fulfilling this criterion if they show a change from baseline to Week 76 in BCVA of greater than or equal to 15 letters.

All subjects who drop out of the study will be deemed to have not met the co-primary efficacy variable, except for the following:

- If the investigator assesses in a subject who drops out after Week 24 resolution of macular edema secondary to CRVO with no need for further treatment with IVT aflibercept, the change from baseline to the last measurement of BCVA for this subject will be categorized using the last observation carried forward (LOCF) methodology. As proof of permanent resolution of macular edema, at least 1 additional, confirmatory monitoring visit is required (after a minimum of 8 weeks and no later than the Week 76 visit). Any additional CRT and BCVA measurements at subsequent visits need to be consistent with the permanent resolution of macular edema as well. In case these conditions are not fulfilled, the respective subject is considered to have not met the variable.

##### **Definition: Proportion of subjects with a mean treatment interval between injections of $\geq 8$ weeks from the last actual visit of the initiation phase to Week 76**

The co-primary efficacy variable of the proportion of subjects with a mean treatment interval between injections of  $\geq 8$  weeks from the last actual visit of the initiation phase to Week 76 will be assessed as follows:

- For subjects completing the study to Week 76, the mean treatment interval between injections from the last actual visit of the initiation phase to Week 76 will be calculated as follows:



(date of last injection up to and including Week 76 visit – date of last actual visit of initiation phase)/(number of injections taken from last visit of initiation phase until immediately prior to the Week 76 visit – 1)

- Should the mean treatment interval for a subject between injections from the last actual visit of the initiation phase to Week 76 be  $\geq 56$  days, then the mean treatment interval is deemed to be  $\geq 8$  weeks and the co-primary efficacy variable has been met, if the mean is  $< 56$  days, then the co-primary efficacy variable has not been met for this subject.
- All subjects who drop out of the study will be deemed to have not met the co-primary efficacy variable, except for the following:

Subjects who drop out after Week 24 and who are defined by the investigator as having a permanent resolution of macular edema are considered to have met the co-primary efficacy variable. For subjects considered by the investigator to have a permanent resolution of macular edema, at least 1 additional confirmatory visit is required (after a minimum interval of 8 weeks from the visit when resolution was determined and up to the regular Week 76 visit).

The approach to handle discontinued subjects is considered sufficiently conservative with regard to assessing mean treatment interval. The number and percentage of subjects who gain  $\geq 15$  letters in BCVA on the ETDRS chart compared with baseline at the Week 76 variable and the subjects with a mean treatment interval between injections of  $\geq 8$  weeks from the last actual visit of initiation phase to Week 76 will be presented, and, in addition, the mean and median treatment interval and frequency from baseline to Week 76, and during the T&E phase, will be described based on 95% confidence intervals.

#### 10.3.2.2.2 Secondary and exploratory efficacy variables

Analyses of secondary, other, and exploratory efficacy variables will be conducted on the Full Analysis Set as defined in Section 10.2.

The secondary efficacy variables are as follows:

- The change in BCVA as measured by the ETDRS letter score from baseline to Weeks 24, 52, and 76
- The change in CRT from baseline to Weeks 24, 52, and 76
- The number of injections from baseline to Week 76
- The mean treatment interval between injections from baseline to Week 76
- The proportion of subjects who gain  $\geq 15$  letters in BCVA on the ETDRS chart compared with baseline at Weeks 24 and 52
- The change in retinal perfusion (FA/FP) status from screening/baseline<sup>63</sup> to Weeks 24, 52, and 76

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<sup>63</sup>Clarified that assessment of secondary variable of change in retinal perfusion status will include screening/baseline combined visit per Amendment 1, Modification 3 (see Section 15.1.1.3).



- The proportion of subjects with absence of fluid at Weeks 24, 52, and 76

The exploratory variables are as follows:

- Perfusion status of the retina assessed by wide-field at screening/baseline,<sup>64</sup> Weeks 24, 52, and 76
- OCT angiography measures for assessing perfusion status of the retina and examination of morphological changes related to disease progression in CRVO at baseline, Weeks 24, 52, and 76
- Full-field ERG assessments at baseline, Weeks 24, 52, and 76
- Status of RAPD at baseline, Weeks 24, 52, and 76

For other efficacy variables, with regard to proportion of responder-based variables, subjects discontinued until the respective time point will be considered as non-responders (if no proof of permanently resolved macular edema exists). For change from baseline-based variables, missing data will be imputed by means of LOCF method. Sensitivity analyses for these variables will be provided based on the multiple imputation method as outlined in the SAP. In addition, observed case-based analyses will be provided for secondary efficacy variables.

For those variables for which change will be evaluated, 95% confidence intervals based on t-distribution-based methodology will be provided.

For the change in retinal perfusion status, the number of subjects perfused at baseline will be compared with the number of subjects perfused at Weeks 24, 52, and 76, by means of 95% confidence intervals using exact McNemar methodology. Similar approaches will be used for variables regarding proportions of subjects, if applicable.

More details on tests with regard to statistical analysis (going beyond what is described in Section 10.3.2.2.3) of the co-primary, secondary, and exploratory efficacy variables, including sensitivity analyses, will be provided in the SAP.

#### 10.3.2.2.3 Statistical test

By means of evaluating both co-primary variables, the exact 1-sample binomial test will be used for both co-primary variables.

Study success requires to prove that both a gain of  $\geq 15$  letters in BCVA at Week 76 is reached by at least 40% of subjects, and, additionally, at least 50% of subjects have a mean treatment interval of  $\geq 8$  weeks in the T&E phase.

In further explanations, the null hypothesis for evaluation of the co-primary variable 1 (proportion of subjects with gain of  $\geq 15$  letters in BCVA at Week 76) will be labeled as  $H_{01}$ , the alternative hypothesis as  $H_{11}$ .

Similarly, for evaluation of the co-primary variable 2 (proportion of subjects with a mean treatment interval of  $\geq 8$  weeks), the null-hypothesis will be labeled as  $H_{02}$ , while the alternative hypothesis will be labeled as  $H_{12}$ .

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<sup>64</sup> Exploratory variable assessment clarified to include screening/baseline combined visit per Amendment 1, Modification 9 (see Section 15.1.1.9).

Then, the primary hypothesis  $H_0$  will be tested statistically, as:

- $H_0: H_{01}: p_1 < 40\%$                       or             $H_{02}: p_2 < 50\%$  versus
- $H_1: H_{11}: p_1 \geq 40\%$                       and             $H_{12}: p_2 \geq 50\%$

Where  $p_1$  is the proportion of subjects with a  $\geq 15$ -letter gain in BCVA at Week 76, while  $p_2$  is the proportion of subjects with a mean treatment interval of  $\geq 8$  weeks. The significance level  $\alpha$  for this 2-sided test will be 5%.

Given the statistical paradigm of the intersection-union test, the test on  $H_0$  can be performed as independent statistical tests on  $H_{01}$  and  $H_{02}$ .

The subgroup of subjects having a mean treatment interval of  $\geq 8$  weeks will be analyzed with regard to gain of  $\geq 15$  letters in BCVA at Week 76 as a sensitivity analysis.

The primary study result will be from the evaluation of the co-primary efficacy variables, based on the Full Analysis Set.

### 10.3.2.3 Safety analysis

The safety analysis will be conducted in the Safety Analysis Set. Treatment-emergent AEs will be presented by MedDRA preferred term within primary system organ class and summarized. Intensity and causal relationship to the investigational product will be analyzed descriptively. Serious AEs, including narratives, will be documented separately.

Other safety variables (e.g. IOP measurements and vital signs) will be analyzed descriptively including changes from baseline.

### 10.3.3 Missing data/dropouts

Data from subjects who drop out of the study will be included in all summaries where possible.

Further details are provided in the SAP.

## 10.4 Determination of sample size

Sample size estimation was performed with PASS (Power Analysis and Sample Size) software, version 11.

For the overall power of the study to reach  $\geq 90\%$ , the required power for each of the 2 co-primary efficacy tests has to be  $\geq 94.9\%$ , resulting from the intersection-union test strategy.

For the co-primary efficacy variable related to the proportion of subjects with a  $\geq 15$ -letter gain in BCVA at Week 76, to detect a proportion of at least 40% (null hypothesis  $H_0: p[\geq 15 \text{ letters}] < 40\%$ ), 150 fully evaluable subjects result in a power to reject this co-primary null-hypothesis of 94.9% (under assumption of true proportion in population of 55%).<sup>65</sup>

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<sup>65</sup> In the GALILEO trial, the percentage of subjects with  $\geq 15$  letter gain until Week 76 (in the aflibercept-treated arm) was 57.3%. (footnote to text; not a modification)

For the co-primary efficacy variable related to proportion of subjects with a mean treatment interval of  $\geq 8$  weeks in the T&E phase at Week 76, to detect a proportion of at least 50% (null hypothesis  $H_0: p[\geq 8 \text{ weeks}] < 50\%$ ), 150 fully evaluable subjects result in a power to reject this co-primary null-hypothesis of 95.5% (under assumption of true proportion in population of 65%).<sup>66</sup>

The study power to have a significant primary result (i.e. significant result in both co-primary variables) is therefore  $94.93\% * 95.52\% = 90.68\%$ .

The dropout rate before Week 24 is considered to be about 6.5%,<sup>67</sup> resulting in a recruitment of 160 subjects to have 150 fully evaluable subjects in the T&E phase.

No additional subjects to account for dropouts are required.

A sufficient number of subjects will be screened to enroll 160 subjects plus 60 volunteers for SD-OCT/FA/FP certification.

## 10.5 Planned interim analyses

No interim analysis is planned.

## 11. Data handling and quality assurance

### 11.1 Data recording

The data collection tool for this study will be a validated electronic data capture (EDC) system called RAVE. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system.

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE that Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. The CRO extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer, CRO, and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are to be maintained.

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<sup>66</sup> Post-hoc evaluations on the GALILEO trial data had shown that about 65% of subjects had a treatment interval of  $\geq 8$  weeks (in the PRN phase of GALILEO). (*footnote to text; not a modification*)

<sup>67</sup> Expected dropout rate, taking into account dropout behavior in the GALILEO trial until Weeks 24 (for aflibercept-treated arm). (*footnote to text; not a modification*)

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made, and the date and time it was made. This information is available both at the investigator's site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all subjects enrolled in this study.

### **Source documentation**

It is the expectation of the sponsor that data entered into the eCRF has source documentation available at the site. All data must be available in source documents before entry into eCRFs. 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.

### **Data recorded from screening failures**

Data of "only screened subjects" will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At minimum, the following data should be recorded in the eCRF:

- Demographic information (subject number; year of birth/age; sex; if applicable race/ethnicity)
- Date of informed consent
- Reason for premature discontinuation
- Date of last visit

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the eCRF in addition to the data specified above:

- All information related to the SAE such as:
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary page

## **11.2 Monitoring**

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's

requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate, and complete. Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol).
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

### 11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g. laboratory, electrocardiogram, adjudication committees).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

### 11.4 Missing data

Most important is to avoid missing data by monitoring in time for completeness (Section 10.3.2.2.1) and investigators' training, especially to motivate subjects to be compliant with the study protocol.

Moreover, the risk of bias to the efficacy results due to missing data may be decreased in this study, since all subjects will receive IVT aflibercept during the course of this study. With regard to primary efficacy, discontinued subjects will be handled as defined in Section 10.3.2.2.1.

### 11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IECs/IRBs are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

## 11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Subject (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution, or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

## 12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due to, but not limited to, the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of parallel clinical studies
  - Results of parallel animal studies (e.g. on toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; dropout rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IECs/IRBs; competent authority[ies]; study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing subjects, including those in post-study follow-up, must be taken care of in an ethical manner.

Details for an individual subject's withdrawal can be found in Section 6.3.1.

## 13. Ethical and legal aspects

### 13.1 Investigator(s) and other study personnel – amended

All other study personnel are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained, and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

#### Central reading center for images

An independent central reading center will evaluate the ophthalmic images defined in Section 9.<sup>68</sup>

#### External data evaluation bodies

The sponsor may decide to institute a Steering Committee to guide the trial in all aspects of safety and efficacy and must ensure that all relevant information is provided by investigators. The composition of the team, the functional roles, and responsibilities will be specified in the Charter.<sup>69</sup>

Finally, an adjudication committee will perform an additional analysis of arterial thrombotic events (ATEs) based on the Antiplatelet Trialists' Collaboration (APTC) endpoint of non-fatal myocardial infarction, non-fatal stroke, and fatal vascular events, including fatal hemorrhages and sudden unexplained death. Details will be described in the Adjudication Committee Charter.<sup>70</sup>

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<sup>68</sup> Added that ophthalmic images will be evaluated by an independent central reading center per Amendment 1, Modification 34 (see Section 15.1.1.34).

<sup>69</sup> Steering Committee may be used to guide the study; responsibilities will be outlined in the Charter per Amendment 1, Modification 35 (see Section 15.1.1.35).

<sup>70</sup> An Adjudication Committee will perform additional analysis of arterial thrombotic events based on the listed APTC endpoints per Amendment 1, Modification 36 (see Section 15.1.1.36).



## 13.2 Funding and financial disclosure

### Funding

This study will be funded by its sponsor.

### Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

## 13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IECs/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations, and organizations. When necessary, an extension, amendment, or renewal of the IEC/IRB approval must be obtained and forwarded to the sponsor. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the EC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

## 13.4 Subject information and consent

All relevant information on the study will be summarized in integrated subject information sheets and ICFs provided by the sponsor. A sample subject information and ICF is provided as a document separate to this protocol.



Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject/legal representative or proxy consentor (if the subject is under legal protection) prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each subject/legal representative or proxy consentor will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's consent covers end-of-study examinations as specified in the visit description in Section 9.2.5 to be conducted after withdrawal of consent.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the SAP.
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine, or tissues); these data would also be retained and statistically analyzed in accordance with the SAP. The subject has the right to object to the generation and processing of this post-withdrawal data. For this, he/she needs to sign a corresponding declaration of objection; alternatively, the subject's oral objection may be documented in the subject's source data.

Each subject/legal representative or proxy consentor will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject/legal representative or proxy consentor voluntarily agrees to sign the ICF and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject/legal representative or proxy consentor will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the subject's note/file of the medical institution.

In the event that informed consent is obtained on the date that screening study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

If the subject is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

For adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested where such a person is able to



express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

The ICF and any other written information provided to subjects/legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and/or the written ICF. The investigator will inform the subject/legal representative or proxy consenters of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IEC/IRB's approval/favorable opinion in advance of use.

### **13.5 Publication policy and use of data**

The sponsor has made the information regarding the study protocol publicly available on the internet at [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

### **13.6 Compensation for health damage of subjects/insurance**

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

### **13.7 Confidentiality**

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the



information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

## 14. Reference list

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<sup>71</sup> Reference list change, SmPC replaced Investigator’s Brochure and moved from reference list 13 to 2 per Amendment 1, Modification 15.1.1.4 (see Section 15.1.1.4).



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<sup>72</sup> Reference removed for Thompson HS, et al per Amendment 1, Modification 15.1.1.33 (see Section [15.1.1.33](#)).

## 15. Protocol amendments

### Editorial note

In the Section 15.1.2 on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version. As applicable, changes to the protocol text are indicated as follows:

- **Addition of a whole new portion:** Brief identification of the new portion
- **Removal of a whole portion:** Complete display of the removed portion, formatted as ~~crossed-out~~
- **Editing of an existing portion:** Comparative presentation of “Old text” versus “New text”, with “Old text” referring to the most recent previous protocol version. Deletions are ~~crossed-out~~ in the “Old text”. Additions are underlined in the “New text”.
- **Tables/figures:** The term “amended” is added to the caption.
- **Terminological changes:** Brief specification of the terminological change

Corrections of typos or omissions are not highlighted.

### 15.1 Amendment 1, dated 20 Apr 2016

#### 15.1.1 Overview of changes to the study

##### 15.1.1.1 Modification 1: Adjustments to Treat and Extend treatment interval

Wording change from “will be adjusted” to “may be adjusted”.

Rationale: To clarify that frequency of injections may be adjusted to maintain stable visual and anatomic outcomes.

The following protocol sections are affected by this modification:

Synopsis Section Methodology

Section 7.1.1 Treat and Extend treatment visits

Table 9-1 Schedule of Evaluations and Study Procedures

##### 15.1.1.2 Modification 2: Subjects discontinued from treatment with indications of worsening

Deleted text stating that subjects discontinued from treatment for not benefiting from continued treatment may resume treatment if retreatment criteria indicate worsening.

Rationale: To clarify that subjects who are withdrawn do not need to be followed-up.

The following protocol sections are affected by this modification:

Synopsis Section Methodology

Table 9-1 Schedule of Evaluations and Study Procedures

### 15.1.1.3 Modification 3: Secondary variable change in retinal perfusion status

Secondary efficacy variable of change in retinal perfusion (FA/FP) status will be assessed from screening/baseline to Weeks 24, 52, and 76.

Rationale: Clarified that secondary variable of change in retinal perfusion status will include data from screening/baseline combined visit.

The following protocol sections are affected by this modification:

- Synopsis Section Variables
- Section 5 Study design
- Section 9.4.2 Secondary efficacy variables
- Table 9-2 Schedule of Efficacy Variable Assessments
- Section 10.3.2.2.2 Secondary and exploratory efficacy variables

### 15.1.1.4 Modification 4: Reference change

Reference list change, SmPC replaced Investigator's Brochure and moved from reference list 13 to 2.

Rationale: SmPC relevant (replaced Investigator's Brochure)

The following protocol sections are affected by this modification:

- Section 3 Introduction
- Section 14 Reference list

### 15.1.1.5 Modification 5: Visits for screening and baseline

Screening and baseline visits can be combined.

Rationale: Clarification and correction of text to align with other sections of the protocol.

The following protocol section is affected by this modification:

- Section 5 Study design

### 15.1.1.6 Modification 6: Time point for follow-up

Subjects will continue to be followed to Week 76 or until follow-up is no longer possible.

Rationale: Correction of text to clarify that follow-up to Week 76 is necessary, regardless of whether subject requires further injections, providing that follow-up is possible (i.e. subject is not lost to follow-up or prematurely discontinued).

The following protocol section is affected by this modification:

- Section 5 Study design

### 15.1.1.7 Modification 7: Window for post-baseline study visits

A  $\pm$  7-day window will be allowed for all post-baseline visits.

Rationale: For consistency among all post-baseline visits.



The following protocol sections are affected by this modification:

Section 5 Study design

Table 9-1 Schedule of Evaluations and Study Procedures

Section 9.2.4.1 Treat and Extend visits

Section 10.3.1 Variables

#### **15.1.1.8 Modification 8: Examinations based on investigator's medical judgment and standard of care**

Examinations that may be performed at other times during the 76 weeks of the study based on the investigator's medical judgment and standard of care include FA/FP, wide-field FA, OCT angiography, and full-field ERG.

Rationale: Specified ERG is full-field and added wide-field FA and OCT angiography examinations that may be performed at other times during the study based on the investigator's medical judgment and standard of care.

The following protocol sections are affected by this modification:

Section 5 Study design

Table 9-1 Schedule of Evaluations and Study Procedures

#### **15.1.1.9 Modification 9: Exploratory variable perfusion status of retina**

Exploratory variable of perfusion status of the retina will be assessed by wide-field FA at screening/baseline, Weeks 24, 52, and 76.

Rationale: Clarified that assessment of exploratory variable of perfusion status of the retina by wide-field FA will include screening/baseline combined visit.

The following protocol sections are affected by this modification:

Section 5 Study design

Section 9.4.3 Exploratory efficacy variables

Table 9-2 Schedule of Efficacy Variable Assessments

Section 10.3.2.2.2 Secondary and exploratory efficacy variables

#### **15.1.1.10 Modification 10: Study end**

The last visit of the last subject (end of the study) includes the safety follow-up period.

Rationale: To clarify the time point for the end of the study.

The following protocol section is affected by this modification:

Section 5 Study design

#### **15.1.1.11 Modification 11: Final study visit**

Completion of the final study visit at Week 76 includes the mandatory safety follow-up contact.

Rationale: To clarify the time point for completion of the final study visit.

The following protocol section is affected by this modification:

Section 5 Study design

#### **15.1.1.12 Modification 12: Assessment of eligibility**

Eligibility criteria based on OCT assessment, BCVA, and FA and FP do not need to be repeated at the baseline visit.

Rationale: To clarify that assessment of eligibility criteria based on OCT assessment, BCVA and FA and FP is not required at the baseline visit if these assessments are performed at the initial/screening.

The following protocol section is affected by this modification:

Section 6 Study population

#### **15.1.1.13 Modification 13: Exclusion criterion 22**

Exclusion criteria AMD types are neovascular AMD or geographic atrophy.

Rationale: Types of AMD defined.

The following protocol section is affected by this modification:

Section 6.2 Exclusion criteria

#### **15.1.1.14 Modification 14: Rescreening**

Added that subjects may be rescreened if reason for initial screening failure was resolved within 30 days of initial screening.

Rationale: To clarify rescreening criteria.

The following protocol section is affected by this modification:

Section 6.3.1 Withdrawal

#### **15.1.1.15 Modification 15: Rescreening for inclusion/exclusion criteria**

Removed examples of exclusion criteria.

Rationale: For clarity, examples are mentioned above.

The following protocol section is affected by this modification:

Section 6.3.1 Withdrawal

#### **15.1.1.16 Modification 16: Stability criteria**

The time period for stability criteria is reworded from “previous last visit” to “second to last visit.”

Rationale: For clarity.

The following protocol sections are affected by this modification:

Section 7.1.2 Stability criteria

**15.1.1.17 Modification 17: Dose preparation**

Removed text stating that dose must be administered within 2 hours of start of dose preparation.

Rationale: In accordance with updated drug information.

The following protocol sections are affected by this modification:

Section 7.4 Dosage and administration

Appendix 16.1 Intravitreal aflibercept injection procedure

**15.1.1.18 Modification 18: Disposal of study drug**

Added that a sponsor designee may approve disposal of drug at the site and removed that study drug may be returned to the sponsor for disposal.

Rationale: Correction of process for disposal of study drug.

The following protocol section is affected by this modification:

Section 7.5 Drug logistics and accountability

**15.1.1.19 Modification 19: Rescue therapy**

Removed conditions when subjects may receive PRP rescue, and added that subjects may receive PRP rescue per investigator discretion.

Rationale: Clarified that PRP rescue may be used per investigator discretion.

The following protocol section is affected by this modification:

Section 8.1 Prior and concomitant therapy

**15.1.1.20 Modification 20: Screening/baseline procedures**

Procedures may be performed on separate days if screening and baseline visits are combined; however, procedures for slit lamp (anterior segment), IOP measurement, and indirect ophthalmoscopy are recommended to take place/be repeated on the same day as the IVT injection.

Rationale: Clarified that subjects do not need to undergo all procedures on same day if screening and baseline are combined and specified procedures recommended to take place on same day as IVT injection.

The following protocol sections are affected by this modification:

Table 9-1 Schedule of Evaluations and Study Procedures

Section 9.2 Visit descriptions

**15.1.1.21 Modification 21: Window for screening/baseline assessments**

For the baseline and screening visits to be considered a combined visit, the assessments must take place within a 7-day window.

Rationale: To clarify that assessments for screening/baseline combined visit must be completed within a 7-day period.

The following protocol sections are affected by this modification:

Table 9-1 Schedule of Evaluations and Study Procedures

Section 9.2 Visit descriptions

#### **15.1.1.22 Modification 22: Post-baseline visit procedures**

Post-baseline visits may be split, but procedures required at each visit but must be completed within 7 days; however, procedures for slit lamp (anterior segment), IOP measurement, and indirect ophthalmoscopy are recommended to take place on the same day as the IVT injection.

Rationale: Procedures for each post-baseline visit may be completed on separate days but must be completed within a 7-day period.

The following protocol section is affected by this modification:

Table 9-1 Schedule of Evaluations and Study Procedures

#### **15.1.1.23 Modification 23: Prescheduled visits at Weeks 24 and 52**

Prescheduled visits at Weeks 24 and 52 do not pertain to T&E posology; however, subject may receive IVT injection based on subject's T&E schedule.

Rationale: Clarified that visits at Weeks 24 and 52 are not considered part of the T&E posology.

The following protocol section is affected by this modification:

Table 9-1 Schedule of Evaluations and Study Procedures

#### **15.1.1.24 Modification 24: Pregnancy testing**

Pregnancy testing is mandatory for women of childbearing potential at every treatment visit prior to injection and at End of Study visit if required by local regulations.

Rationale: Added visits at which pregnancy testing is mandatory if required to accommodate local regulatory requirements.

The following protocol sections are affected by this modification:

Table 9-1 Schedule of Evaluations and Study Procedures

Section 9.2.2 Baseline visit (Visit 2, Day 1)

Section 9.2.3 Initiation phase (2Q4 treatment intervals  $\pm$  7 days)

Section 9.2.4.1 Treat and Extend visits

Section 9.2.4.2 Week 24 ( $\pm$  7 days) interim visit

Section 9.2.4.3 Week 52 ( $\pm$  7 days) interim visit

Section 9.6.3.1 Pregnancy test

**15.1.1.25 Modification 25: Fluorescein angiography and fundus photography at baseline visit**

If there is no significant change in indirect ophthalmoscopy, an additional FA/FP at baseline is not required.

Rationale: Clarified that FA/FP examination at baseline is not necessary if indirect ophthalmoscopy does not indicate change.

The following protocol sections are affected by this modification:

Table 9-1 Schedule of Evaluations and Study Procedures

Section 9.2.2 Baseline visit (Visit 2, Day 1)

**15.1.1.26 Modification 26: Fluorescein angiography and fundus photography combined with wide-field examinations**

When possible, FA/FP examinations can be combined with wide-field examination and separate fluorescein injection should be avoided.

Rationale: For clarification that FA/FP examinations combined with wide-field examinations to avoid separate fluorescein injection.

The following protocol sections are affected by this modification:

Table 9-1 Schedule of Evaluations and Study Procedures

Section 9.2.2 Baseline visit (Visit 2, Day 1)

Section 9.4.4.3 Fluorescein angiography and fundus photography

**15.1.1.27 Modification 27: Telephone safety contact with investigator at 30 days post-dose**

Mandatory telephone safety contact with the investigator 30 days after last dose of study drug.

Rationale: Reworded for clarity.

The following protocol sections are affected by this modification:

Table 9-1 Schedule of Evaluations and Study Procedures

Section 9.2.4.4 Week 76 ( $\pm$  7 days) final study visit

Section 9.2.5 Early termination visit

**15.1.1.28 Modification 28: Assessments at initial visit**

Specified assessments that should be performed at the initial visit when screening/baseline visits are combined.

Rationale: Clarified testing that should take place when subject is first seen if screening and baseline visits are combined.

The following protocol sections are affected by this modification:

Table 9-1 Schedule of Evaluations and Study Procedures

Section 9.2 Visit descriptions

Section 9.2.2 Baseline visit (Visit 2, Day 1)

Table 9-2 Schedule of Efficacy Variable Assessments

Section 9.4.4.4 Wide-field fluorescein angiography

Section 9.4.4.5 Optical coherence tomography angiography

Section 9.4.4.6 Full-field electroretinography

#### **15.1.1.29 Modification 29: Gonioscopy order of procedure**

Removed wording that gonioscopy is performed after OCT and before FA/FP.

Rationale: Not necessary to specify order in which gonioscopy is performed.

The following protocol sections are affected by this modification:

Table 9-1 Schedule of Evaluations and Study Procedures

Section 9.6.3.4.4 Gonioscopy

#### **15.1.1.30 Modification 30: Post-treatment safety telephone calls**

Schedule for safety follow-up telephone calls changed from 3 days after treatment to within 3 days.

Rationale: Addition made to allow flexibility for time of post-treatment safety follow-up calls.

The following protocol sections are affected by this modification:

Table 9-1 Schedule of Evaluations and Study Procedures

Section 9.2.2 Baseline visit (Visit 2, Day 1)

Section 9.2.3 Initiation phase (2Q4 treatment intervals ( $\pm 7$  days))

Section 9.2.4.1 Treat and Extend visits

Section 9.2.4.2 Week 24 ( $\pm 7$  days)

Section 9.2.4.3 Week 52 ( $\pm 7$  days) interim visit

Appendix 16.1 Intravitreal aflibercept injection procedure

#### **15.1.1.31 Modification 31: Grammatical correction “pertain”**

Wording changed from “is not a visit pertaining” to “does not pertain” in reference to T&E posology.

Rationale: Grammatical correction.

The following protocol sections are affected by this modification:

Table 9-1 Schedule of Evaluations and Study Procedures

Section 9.2.4.2 Week 24 ( $\pm 7$  days)

Section 9.2.4.3 Week 52 ( $\pm 7$  days) interim visit

Section 9.2.4.4 Week 76 ( $\pm$  7 days) final study visit

#### **15.1.1.32 Modification 32: Early termination visit**

Removed sentence describing monitoring interval if subject is withdrawn from the study.

Rationale: Did not pertain to early termination visit.

The following protocol section is affected by this modification:

Section 9.2.5 Early termination visit

#### **15.1.1.33 Modification 33: Reference removed**

Removed reference to Thompson HS, et al.

Rationale: Not relevant.

The following protocol sections are affected by this modification:

Section 9.6.3.5 Investigator(s) and other study personnel

Section 14 Reference List

#### **15.1.1.34 Modification 34: Central reading center for images**

Added that ophthalmic images will be evaluated by an independent central reading center.

Rationale: To clarify that an independent central reading center will evaluate images.

The following protocol section is affected by this modification:

Section 13.1 Investigator(s) and other study personnel

#### **15.1.1.35 Modification 35: Steering Committee**

Steering Committee may be used to guide the study; responsibilities will be outlined in the Charter.

Rationale: Identified that study may be overseen by a Steering Committee.

The following protocol section is affected by this modification:

Section 13.1 Investigator(s) and other study personnel

#### **15.1.1.36 Modification 36: Adjudication committee**

An Adjudication Committee will perform additional analysis of arterial thrombotic events based on the listed APTC endpoints.

Rationale: Added that an Adjudication Committee will be used for additional analysis.

The following protocol section is affected by this modification:

Section 13.1 Investigator(s) and other study personnel

#### **15.1.1.37 Modification 37: Study drug vials**

Study drug will be supplied in 2-mL vials.

Rationale: Correction of text in accordance with study drug vials to be supplied.

The following protocol section is affected by this modification:

Section 16.1 Intravitreal aflibercept injection procedure

### **15.1.2 Changes to the protocol text**

Changes to the protocol text are indicated as specified at the beginning of Section 14.

#### **15.1.2.1 Adjustments to Treat and Extend treatment interval - Synopsis section Methodology**

Wording change from “will be adjusted” to “may be adjusted” to clarify that frequency of injections may be adjusted to maintain stable visual and anatomic outcomes per Modification 1 (Section 15.1.1.1).

##### **Old text**

Starting at Week 8, the stability criteria will be evaluated and the frequency of injections ~~will~~ be adjusted (increased or decreased by 2-week intervals) to maintain stable visual and anatomic outcomes.

##### **New text**

Starting at Week 8, the stability criteria will be evaluated and the frequency of injections may be adjusted (increased or decreased by 2-week intervals) to maintain stable visual and anatomic outcomes.

#### **15.1.2.2 Subjects discontinued from treatment with indications of worsening - Synopsis section Methodology**

Deleted text stating that subjects discontinued from treatment for not benefiting from continued treatment may resume treatment if retreatment criteria indicate worsening

##### **Old text**

~~If it is determined by the investigator (in the investigator’s best judgment) that the subject is not benefiting from continued treatment or if the investigator considers the subject to have permanent resolution of macular edema, treatment may be discontinued, but monitoring should be continued with a follow-up visit at a minimum interval of 8 weeks and at all subsequent prescheduled visits (i.e. Weeks 24, 52, and 76). Treatment should be resumed if the retreatment criteria indicate worsening (i.e. at least 1 criterion for deterioration is met).~~

##### **New text**

If the investigator considers the subject to have permanent resolution of macular edema, treatment may be discontinued, but monitoring should be continued with a follow-up visit at a minimum interval of 8 weeks and at all subsequent prescheduled visits (i.e. Weeks 24, 52, and 76). Treatment should be resumed if the retreatment criteria indicate worsening (i.e. at least 1 criterion for deterioration is met).



### 15.1.2.3 Secondary variable change in retinal perfusion status – Synopsis Section Variables

Clarified that assessment of secondary variable of change in retinal perfusion status will include screening/baseline combined visit per Modification 2 (Section 15.1.1.2).

#### Old text

- The change in retinal perfusion (FA/FP) status from baseline to Weeks 24, 52 and 76

#### New text

- The change in retinal perfusion (FA/FP) status from screening/baseline to Weeks 24, 52 and 76

### 15.1.2.4 Reference change – Section 3 Introduction

Citation for reference to SmPC applied per Modification 3 (Section 15.1.1.4).

#### Old text

Further details are provided in the applicable SmPC.

#### New text

Further details are provided in the applicable Summary of Product Characteristics (SmPC) (2)

### 15.1.2.5 Visits for screening and baseline – Section 5 Study design

Clarified that screening and baseline visits can be combined per Modification 4 (Section 15.1.1.5).

#### Old text

The initial screening visit must be within the enrollment period in the respective country (i.e. no retrospective inclusion). Subjects must give written informed consent prior to any data documentation. Subjects will receive the first study treatment at the baseline visit on Day 1. ~~Screening and baseline need to be separate visits in order to confirm the inclusion/exclusion criteria.~~

#### New text

The initial screening visit must be within the enrollment period in the respective country (i.e. no retrospective inclusion). Subjects must give written informed consent prior to any data documentation. Subjects will receive the first study treatment at the baseline visit on Day 1.

### 15.1.2.6 Time point for follow-up – Section 5 Study design

Clarified that follow-up to Week 76 is necessary, regardless of whether subject requires further injections, providing that follow-up is possible per Modification 6 (Section 15.1.1.6).

#### Old text

Subjects will be followed for a time period of 76 weeks or until follow-up is no longer ~~necessary or possible~~.

**New text**

Subjects will be followed for a time period of 76 weeks or until follow-up is no longer possible.

**15.1.2.7 Window for post-baseline study visits – Section 5 Study design**

Clarified that a  $\pm 7$ -day window will be allowed for all post-baseline visits per Modification 7 (Section 15.1.1.7).

**Old text**

This study comprises a screening period of up to 21 days and a treatment period of 76 weeks. There will be prescheduled visits at baseline, Weeks 24, 52, and 76 (end-of-study visit). ~~The visit schedules at Weeks 24, 52, and 76 may deviate by  $\pm 7$  days.~~ Other visits between baseline and Week 76 will depend on the applied posology of IVT aflibercept and the monitoring schedule for each subject.

**New text**

This study comprises a screening period of up to 21 days and a treatment period of 76 weeks. There will be prescheduled visits at baseline, Weeks 24, 52, and 76 (end-of-study visit). Other visits between baseline and Week 76 will depend on the applied posology of IVT aflibercept and the monitoring schedule for each subject. A  $\pm 7$ -day window will be allowed for all post-baseline visits.

**15.1.2.8 Examinations based on investigator's medical judgment and standard of care – Section 5 Study design**

Specified ERG is full-field and added wide-field FA and OCT angiography examinations that may be performed at other times during the study based on the investigator's medical judgment and standard of care per Modification 8 (Section 15.1.1.8).

**Old text**

However, the treating investigator may perform ~~FA/FPs or ERGs~~ at other times during the 76 weeks of study treatment based on his/her medical judgment and standard of care.

**New text**

However, the treating investigator may perform FA/FP, wide-field FA, OCT angiography, or full-field ERG at other times during the 76 weeks of study treatment based on his/her medical judgment and standard of care.

**15.1.2.9 Study end – Section 5 Study design**

Clarified that the last visit of the last subject (end of the study) includes the safety follow-up period per Modification 10 (Section 15.1.1.10).

**Old text**

The end of the study as a whole will be reached as soon as the last visit of the last subject is reached in all centers in all participating countries (EU and non-EU).

**New text**

The end of the study as a whole will be reached as soon as the last visit of the last subject, including safety follow-up, is reached in all centers in all participating countries (EU and non-EU).

**15.1.2.10 Final study visit – Section 5 Study design**

Clarified that completion of the final study visit at Week 76 includes the mandatory safety follow-up contact per Modification 11 (Section 15.1.1.11).

**Old text**

The primary completion event for this study is the final study visit at Week 76.

**New text**

The primary completion event for this study is the final study visit at Week 76, including the mandatory safety follow-up contact.

**15.1.2.11 Secondary variable change in retinal perfusion status – Section 5 Study design**

Clarified that assessment of secondary variable of change in retinal perfusion status will include screening/baseline combined visit per Modification 3 (Section 15.1.1.2).

**Old text**

- The change in retinal perfusion (FA/FP) status from baseline to Weeks 24, 52, and 76

**New text**

- The change in retinal perfusion (FA/FP) status from screening/baseline to Weeks 24, 52, and 76

**15.1.2.12 Exploratory variable perfusion status of retina – Section 5 Study design**

Exploratory variable assessment clarified to include screening/baseline combined visit per Modification 9 (Section 15.1.1.9).

**Old text**

- Perfusion status of the retina assessed by wide-field FA at baseline, Weeks 24, 52, and 76

**New text**

- Perfusion status of the retina assessed by wide-field FA at screening/baseline, Weeks 24, 52, and 76

**15.1.2.13 Assessment of eligibility – Section 6 Study population**

Clarified that assessment of eligibility criteria based on OCT assessment, BCVA and FA and FP is not required at the baseline visit if these assessments are performed at the initial/screening per Modification 12 (Section 15.1.1.12).

**Old text**

In order to be enrolled into this study, a subject must meet ALL of the eligibility criteria. ~~Assessment of eligibility criteria based on OCT assessment, BCVA, and FA and FP will be repeated at the baseline visit.~~

**New text**

In order to be enrolled into this study, a subject must meet ALL of the eligibility criteria.

**15.1.2.14 Exclusion criterion 22 – Section 6.2 Exclusion criteria**

Defined types of AMD per Modification 13 (Section 15.1.1.13).

**Old text**

22. History or clinical evidence of diabetic macular edema, ~~age-related macular degeneration (AMD)~~, BRVO, or any retinal vascular disease other than macular edema secondary to CRVO in either eye.

**New text**

22. History or clinical evidence of diabetic macular edema, AMD (neovascular AMD or geographic atrophy), BRVO, or any retinal vascular disease other than macular edema secondary to CRVO in either eye.

**15.1.2.15 Rescreening – Section 6.3.1 Withdrawal**

Added that subjects may be rescreened if reason for initial screening failure was resolved within 30 days of initial screening per Modification 14 (Section 15.1.1.14).

**Old text**

Restarting the defined set of screening procedures to enable the “screening failure” subject’s participation at a later time point is not allowed, with the following exceptions:

- The subject had successfully passed the screening procedures but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The inclusion/exclusion criteria preventing the subject’s initial attempt to participate have been changed (via protocol amendment).

**New text**

Restarting the defined set of screening procedures to enable the “screening failure” subject’s participation at a later time point is not allowed, with the following exceptions:

- The subject had successfully passed the screening procedures but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.



- The inclusion/exclusion criteria preventing the subject's initial attempt to participate have been changed (via protocol amendment).
- The reason for the screening failure was subsequently resolved (e.g. elevated IOP decreases, inflammation or infection resolves) within 30 days.

#### 15.1.2.16 Rescreening for inclusion/exclusion criteria – Section 6.3.1 Withdrawal

Removed examples of exclusion criteria per Modification 15 (Section 15.1.1.15).

##### Old text

However, if a subject fails screening, i.e. does not meet all inclusion criteria or meets 1 or more of the exclusion criteria (~~e.g. increased IOP or BP~~), the subject can be re-screened 1 time, if the reason(s) for the screening failure is(are) resolved.

##### New text

However, if a subject fails screening (i.e. does not meet all inclusion criteria or meets 1 or more of the exclusion criteria), the subject can be re-screened 1 time, if the reason(s) for the screening failure is(are) resolved.

#### 15.1.2.17 Adjustments to Treat and Extend treatment interval – Section 7.1.1 Treat and Extend treatment visits

Wording change to clarify that frequency of injections may be adjusted to maintain stable visual and anatomic outcomes per Modification 1 (Section 15.1.1.1).

##### Old text

Starting ~~at~~ Week 8, the retreatment interval will be determined as described in Section 7.1.3 and the frequency of injections ~~will~~ be adjusted (increased or decreased by 2-week intervals) to maintain stable visual and anatomic outcomes.

##### New text

Starting at Week 8, the retreatment interval will be determined as described in Section 7.1.3 and the frequency of injections may be adjusted (increased or decreased by 2-week intervals) to maintain stable visual and anatomic outcomes.

#### 15.1.2.18 Stability criteria for BCVA – Section 7.1.2 Stability criteria

The time period for the stability criteria of BCVA was reworded for clarity per Modification 16 (Section 15.1.1.16).

##### Old text

- BCVA within a  $\pm 5$  letter “stability corridor” defined by:
  - No more than 5 letters gain since the last or ~~previous~~ last visit
  - No more than 5 letters loss from best previous BCVA at any visit

##### New text

- BCVA within a  $\pm 5$  letter “stability corridor” defined by:

- No more than 5 letters gain since the last or second to last visit
- No more than 5 letters loss from best previous BCVA at any visit

#### 15.1.2.19 Stability criteria for CRT – Section 7.1 Stability criteria

The time period for the stability criteria of CRT was reworded for clarity per Modification 16 (Section 15.1.1.16).

##### Old text

- CRT within a  $\pm 20\%$  “stability corridor” defined by:
  - No more than 20% thickness reduction since the last or ~~previous~~ last visit
  - No more than 0% thickening from best previous CRT at any visit

##### New text

- CRT within a  $\pm 20\%$  “stability corridor” defined by:
  - No more than 20% thickness reduction since the last or second to last visit
  - No more than 20% thickening from best previous CRT at any visit

#### 15.1.2.20 Dose preparation – Section 7.4 Dose age and administration

Removed text stating that dose must be administered within 2 hours of start of dose preparation per Modification 17 (Section 15.1.1.17).

##### Old text

Vials of IVT aflibercept are to be stored at 2°C to 8°C. Do not freeze. Keep the vial in the outer carton to protect it from light. Prior to usage, the unopened vial of IVT aflibercept may be stored at room temperature (below 25°C/77°F) for up to 24 hours. After opening the vial, procedures must take place under aseptic conditions ~~and the dose must be administered within 2 hours of the start of dose preparation.~~

##### New text

Vials of IVT aflibercept are to be stored at 2°C to 8°C. Do not freeze. Keep the vial in the outer carton to protect it from light. Prior to usage, the unopened vial of IVT aflibercept may be stored at room temperature (below 25°C/77°F) for up to 24 hours. After opening the vial, procedures must take place under aseptic conditions.

#### 15.1.2.21 Disposal of study drug – Section 7.5 Drug logistics and accountability

Added that a sponsor designee may approve disposal of drug at the site and removed that study drug may be returned to the sponsor for disposal per Modification 18 (Section 15.1.1.18).

##### Old text

Drug accountability records must be kept current and should contain the dates, quantities, kit numbers, and batch numbers (or lot numbers) of study drug received by the investigator, dispensed or administered to specified subjects, disposed of at the site (disposal at the site



may occur only with a sponsor approval), or returned to the sponsor or a specified designee for disposal.

#### **New text**

Drug accountability records must be kept current and should contain the dates, quantities, kit numbers, and batch numbers (or lot numbers) of study drug received by the investigator, dispensed or administered to specified subjects, disposed of at the site (disposal at the site may occur only with a sponsor or designee approval or by a specified designee).

#### **15.1.2.22 Rescue therapy – Section 8.1 Prior and concomitant therapy**

Removed conditions when subjects may receive PRP rescue, and added that subjects may receive PRP rescue per investigator discretion per Modification 19 (Section 15.1.1.19).

#### **Old text**

All subjects may receive PRP rescue at any time during the study if ~~they progress to anterior segment neovascularization, neovascularization on optic disc, or clinically relevant neovascularization elsewhere in fundus~~ and will continue to be assessed in this study.

#### **New text**

All subjects may receive PRP rescue at any time during the study if deemed necessary by the investigator and will continue to be assessed in this study.



### **15.1.2.23 Schedule of Evaluations and Study Procedures – Table 9-1 Schedule of Evaluations and Study Procedures**

Due to the complexity of changes made to the table per Modification 1 (Section 15.1.1.1), Modification 2 (Section 15.1.1.2), Modification 3 (Section 15.1.1.3), Modification 7 (Section 15.1.1.7), Modification 8 (Section 15.1.1.8), Modification 20 (Section 15.1.1.20), Modification 21 (Section 15.1.1.21), Modification 22 (Section 15.1.1.22), Modification 23 (Section 15.1.1.23), Modification 24 (Section 15.1.1.24), Modification 25 (Section 15.1.1.25), Modification 26 (Section 15.1.1.26), Modification 27 (Section 15.1.1.27), Modification 28 (Section 15.1.1.28), Modification 29 (Section 15.1.1.29), Modification 30 (Section 15.1.1.30), and Modification 31 (Section 15.1.1.31), no footnotes to these changes are added for the new table. Changes to the table are indicated as specified at the beginning of Section 14. Deletions are crossed out in the “Old text”. Additions are underlined in the “New text”.





			Initiation Phase	T&E Phase				
Visit Description	Screening <sup>a</sup>	Baseline <sup>a</sup>	Treatment Every 4 Weeks (2Q4)	T&E Treatment Visits	Interim <sup>b</sup>	Interim <sup>b</sup>	End of Study <sup>b</sup>	Early Termination
Time Point	Visit 1 Day -21 to Baseline	Visit 2 (Day 1)	Visit 3 and following until stability achieved or Week 20 ( $\pm 7$ days)	According to Individual T&E Schedule <sup>e</sup>	Week 24 ( $\pm 7$ days)	Week 52 ( $\pm 7$ days)	Week 76 ( $\pm 7$ days)	
Full-field ERG <sup>f,g,h</sup>		X			X	X	X	X
Wide-field (angle) FA <sup>g,h</sup>		X			X	X	X	X
OCT angiography <sup>g,h</sup>		X			X	X	X	X
Vital signs <sup>m</sup>	X	X	X	X	X	X	X	X
Administration of study treatment <sup>n</sup>		X	X	X	X	X	o	
Telephone safety check <sup>p</sup>		X	X	X	X	X	X	
Evaluation of posology, how disease activity is monitored, including monitoring frequency		X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; FP, fundus photography; IOP, intraocular pressure; OCT, optical coherence tomography; RAPD, relative afferent pupillary defect; SD-OCT; spectral domain optical coherence tomography T&E, Treat and Extend.

Note: Ocular assessments are to be conducted in both eyes unless otherwise indicated.

- a: The screening and baseline visits can be combined if eligibility criteria are met, all inclusion criteria are fulfilled, and none of the exclusion criteria apply. If screening and baseline occur on the same visit, pregnancy test results and reading center evaluations need to be available prior to treatment with study drug at baseline.
- ~~b: Visit schedules at Weeks 24, 52, and 76 may deviate by  $\pm 7$  days. These visits are not pertaining to the T&E posology; however, based on the subject's T&E schedule, the subject may receive IVT injection of study drug.~~
- e: Monitoring will be performed at each injection visit and at Weeks 24, 52, and 76. Starting at Week 8, the stability criteria will be evaluated as described in Section 7.1.2 and the frequency of injections will be adjusted (increased or decreased by 2-week intervals) to maintain stable visual and anatomic outcomes.
- g: Urine pregnancy test for women of child-bearing potential only. If positive, a serum pregnancy test for confirmation should be performed. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential.
- e: Refraction and BCVA using the ETDRS chart is to be performed at each visit.
- f: The treating investigator may perform these examinations at other times during the 76 weeks of the study based on his/her medical judgment and standard of care.
- g: Conduct in both eyes at baseline (FA/FP additionally in both eyes at screening) and in the study eye only at the other visits indicated unless there are signs of vein occlusion in the fellow eye.
- h: Conduct pre- and post-dose as applicable. If a subject receives a study injection, indirect ophthalmoscopy should be conducted post-dose and IOP should be assessed in the



- study eye 30 to 60 minutes after dosing.
- i: Any AE occurring up to 30 days after the last injection of IVT aflibercept is to be documented regardless of the relationship to the study drug or the seriousness of the event, and reported in accordance with this protocol (see Section 9.6.1.3). A mandatory safety ~~patient~~ contact ~~by telephone~~ 30 days after the last administration of study medication ~~by the investigator~~ is scheduled to ensure ~~no AEs have occurred~~.
  - j: Conducted in both eyes (procedure for conducting RAPD testing is provided in the study manual).
  - k: Performed in the study eye only, ~~after OCT and before FA/FP~~. Conducted at screening and at Week 76 and the early termination visit. May be repeated if needed as determined by the investigator.
  - l: Conducted where feasible and available at selected sites; ~~exploratory measures~~.
  - m: Temperature, blood pressure, and heart rate.
  - n: See Appendix 16.1 for an example study drug injection procedure. Note: Study drug will be administered according to the criteria and timing described in Section 7. ~~If it is determined by the investigator (in the investigator's best judgement) that the subject is not benefiting from continued treatment or the investigator considers permanent resolution of macular edema, treatment may be discontinued, but monitoring should be continued with a follow-up visit at a minimum interval of 8 weeks and at all subsequent prescheduled visits (i.e. Weeks 24, 52, and 76).~~
  - o: Subjects may receive treatment of their underlying disease at their physician's discretion at Week 76 after the end-of-study visit and the assessments for all variables are completed.
  - p: A mandatory safety telephone call will be made 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred.

**New text**
**Table 9-1 Schedule of Evaluations and Procedures**

Visit Description	Initiation Phase			T&E Phase				
	Screening <sup>a</sup>	Baseline <sup>a</sup>	Treatment Every 4 Weeks (2Q4) <sup>b</sup>	T&E Treatment Visits <sup>b</sup>	Interim <sup>b,c</sup>	Interim <sup>b,c</sup>	End of Study <sup>b</sup>	Early Termination
Time Point	Visit 1 Day -21 to Baseline	Visit 2 (Day 1)	Visit 3 and following until stability achieved or Week 20 ( $\pm 7$ days)	According to Individual T&E Schedule ( $\pm 7$ days) <sup>d</sup>	Week 24 ( $\pm 7$ days)	Week 52 ( $\pm 7$ days)	Week 76 ( $\pm 7$ days)	
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographic data	X							
Medical/ophthalmic history	X							
Physical examination	X							
Pregnancy test <sup>e</sup>	X	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Refraction and BCVA (ETDRS chart starting at 4 m) <sup>f</sup>	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X
FA/FP <sup>g,h,i</sup>	X	X			X	X	X	X
AEs <sup>j</sup>	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy <sup>k</sup>	X	X	X	X	X	X	X	X
RAPD <sup>l</sup>		X			X	X	X	X
Slit lamp biomicroscopy	X	X	X	X	X	X	X	X
Gonioscopy <sup>m</sup>	X						X	X
IOP <sup>k</sup>	X	X	X	X	X	X	X	X
Full-field ERG <sup>h,ln</sup>	(X)	X			X	X	X	X

			Initiation Phase	T&E Phase				
Visit Description	Screening <sup>a</sup>	Baseline <sup>a</sup>	Treatment Every 4 Weeks (2Q4) <sup>b</sup>	T&E Treatment Visits <sup>b</sup>	Interim <sup>b,c</sup>	Interim <sup>b,c</sup>	End of Study <sup>b</sup>	Early Termination
Time Point	Visit 1 Day –21 to Baseline	Visit 2 (Day 1)	Visit 3 and following until stability achieved or Week 20 (± 7 days)	According to Individual T&E Schedule (± 7 days) <sup>d</sup>	Week 24 (± 7 days)	Week 52 (± 7 days)	Week 76 (± 7 days)	
Wide-field (angle) FA <sup>g,h,i,n</sup>	(X)	X			X	X	X	X
OCT angiography <sup>h,i,n</sup>	(X)	X			X	X	X	X
Vital signs <sup>o</sup>	X	X	X	X	X	X	X	X
Administration of study treatment <sup>p</sup>		X	X	X	(X)	(X)	g	
Telephone safety check <sup>t</sup>		X	X	X	(X)	(X)	X	
Evaluation of posology, how disease activity is monitored, including monitoring frequency		X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X

Abbreviations: AE, adverse event; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein angiography; FP, fundus photography; IOP, intraocular pressure; OCT, optical coherence tomography; RAPD, relative afferent pupillary defect; SD-OCT; spectral domain optical coherence tomography; T&E, Treat and Extend.

Note: Ocular assessments are to be conducted in both eyes unless otherwise indicated.

- a: The screening and baseline visits can be combined if eligibility criteria are met, all inclusion criteria are fulfilled, and none of the exclusion criteria apply. If screening and baseline occur on the same visit, pregnancy test results and reading center evaluations need to be available prior to treatment with study drug. The necessary procedures can be performed on separate days. However, slit lamp (anterior segment), IOP measurement, and indirect ophthalmoscopy are recommended to take place/be repeated on the same day as the IVT injection. There will be a 7-day window allowed for all procedures to be completed for the combined screening/baseline and the baseline visit.
- b: A ± 7-day window will be allowed for all post-baseline visits. The procedures required at each visit have to be completed within 7 days (i.e. split visits are allowed); however, all procedures have to be completed within the ± 7-day window. Slit lamp (anterior segment), IOP measurement, and indirect ophthalmoscopy are recommended to take place on the same day as the IVT injection.
- c: The visits at Weeks 24 and 52 do not pertain to the T&E posology; however, based on the subject's T&E schedule, the subject may receive IVT injection of study drug.
- d: Monitoring will be performed at each injection visit and at Weeks 24, 52, and 76. Starting at Week 8, the stability criteria will be evaluated as described in Section 7.1.2 and the frequency of injections may be adjusted (increased or decreased by 2-week intervals) to maintain stable visual and anatomic outcomes.
- e: Urine pregnancy test for women of child-bearing potential only. If positive, a serum pregnancy test for confirmation should be performed. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. After screening, a urine pregnancy test is mandatory for women of childbearing potential at every treatment visit (prior to injection) in all countries where it is required by local regulations. If required by local regulations, a pregnancy test should be performed for women of childbearing potential at the End of Study visit.
- f: Refraction and BCVA using the ETDRS chart are to be performed at each visit.
- g: If the investigator considers no significant change in indirect ophthalmoscopy, an additional FA/FP is not mandatory at the baseline visit. Traditional FA/FP examinations



can be combined with wide-field examinations if possible. A separate fluorescein injection, especially, should be avoided.

- h: The treating investigator may perform these examinations at other times during the 76 weeks of the study based on his/her medical judgment and standard of care.
- i: Conduct in both eyes at screening/baseline and in the study eye only at the other visits indicated unless there are signs of vein occlusion in the fellow eye.
- j: Any AE occurring up to 30 days after the last injection of IVT aflibercept is to be documented regardless of the relationship to the study drug or the seriousness of the event, and reported in accordance with this protocol (see Section 9.6.1.3). A mandatory telephone safety contact with the investigator 30 days after the last administration of study medication is scheduled to ensure that the patient has not experienced any AEs.
- k: Conduct pre- and post-dose as applicable. If a subject receives a study injection, indirect ophthalmoscopy should be conducted post-dose and IOP should be assessed in the study eye 30 to 60 minutes after dosing.
- l: Conducted in both eyes (procedure for conducting RAPD testing is provided in the study manual). If the screening and baseline visits are combined, these assessments should be performed at the initial visit.
- m: Performed in the study eye only. Conducted at screening and at Week 76 and the early termination visit. May be repeated if needed as determined by the investigator.
- n: Conducted where feasible and available at selected sites. If the screening and baseline visits are combined, these assessments should be performed at the initial visit.
- o: Temperature, blood pressure, and heart rate.
- p: See Appendix 16.1 for an example study drug injection procedure. Note: Study drug will be administered according to the criteria and timing described in Section 7. If the investigator considers permanent resolution of macular edema, treatment may be discontinued, but monitoring should be continued with a follow-up visit at a minimum interval of 8 weeks and at all subsequent prescheduled visits (i.e. Weeks 24, 52, and 76).
- q: Subjects may receive treatment of their underlying disease at their physician's discretion at Week 76 after the end-of-study visit and the assessments for all variables are completed.
- r: A mandatory safety telephone call will be made within 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred.

#### 15.1.2.24 Screening/baseline procedures –Section 9.2 Visit descriptions

Procedures may be performed on separate days if screening and baseline visits are combined per Modification 20 (Section 15.1.1.20).

##### Old text

The screening and baseline visits can be combined if eligibility criteria are met, all inclusion criteria are fulfilled, and none of the exclusion criteria apply.

##### New text

The screening and baseline visits can be combined if eligibility criteria are met, all inclusion criteria are fulfilled, and none of the exclusion criteria apply. The necessary procedures can be performed on separate days.

#### 15.1.2.25 Window for screening/baseline assessments – Section 9.2 Visit descriptions

Clarified that assessments for screening/baseline combined visit must be completed within a 7-day period per Modification 21 (Section 15.1.1.21).

##### Old text

The screening and baseline visits can be combined if eligibility criteria are met, all inclusion criteria are fulfilled, and none of the exclusion criteria apply. If screening and baseline occur on the same visit, pregnancy test results and reading center evaluations need to be available prior to treatment with study drug at baseline.

##### New text

The screening and baseline visits can be combined if eligibility criteria are met, all inclusion criteria are fulfilled, and none of the exclusion criteria apply. The necessary procedures can be performed on separate days. There will be a 7-day window allowed for all procedures to be completed in such a combined visit. If screening and baseline occur on the same visit, pregnancy test results and reading center evaluations need to be available prior to treatment with study drug.

#### 15.1.2.26 Assessments at initial visit – Section 9.2 Visit descriptions

Clarified when procedures should be performed if screening and baseline visits are combined per Modification 28 (Section 15.1.1.28).

##### Old text

If screening and baseline occur on the same visit, pregnancy test results and reading center evaluations need to be available prior to treatment with study drug at baseline.

##### New text

If screening and baseline occur on the same visit, pregnancy test results and reading center evaluations need to be available prior to treatment with study drug. Furthermore, the additional examinations at baseline should be performed at the initial visit prior to treatment with study drug if the investigator intends to combine screening and baseline visit.



### 15.1.2.27 Pregnancy testing – Section 9.2.2 Baseline visit (Visit 2, Day 1)

Added that pregnancy testing is mandatory to accommodate local regulatory or institutional requirements per Modification 24 (Section 15.1.1.24).

#### Old text

- Confirm inclusion criteria and exclusion criteria. This includes a negative pregnancy test for women of childbearing potential. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential.

#### New text

- Confirm inclusion criteria and exclusion criteria. This includes a negative pregnancy test for women of childbearing potential. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential.
- A urine pregnancy test is mandatory prior to injection for women of childbearing potential in all countries where it is required by local regulations.

### 15.1.2.28 Fluorescein angiography and fundus photography at baseline visit – Section 9.2.2 Baseline visit (Visit 2, Day 1)

Added that an additional FA/FP at baseline is not required if there is no significant change in indirect ophthalmoscopy per Modification 25 (Section 15.1.1.25).

#### Old text

- Ocular assessments (to be conducted in both eyes unless otherwise indicated):
  - Refraction and BCVA using the ETDRS chart (to be performed at each visit)
  - SD-OCT
  - IOP
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - RAPD test
  - FA/FP (the study manual will further specify the standards for FA/FP during the study)

#### New text

- Ocular assessments (to be conducted in both eyes unless otherwise indicated):
  - Refraction and BCVA using the ETDRS chart (to be performed at each visit)
  - SD-OCT
  - IOP
  - Indirect ophthalmoscopy





- Slit lamp biomicroscopy
- RAPD test
- FA/FP (the study manual will further specify the standards for FA/FP during the study). If the investigator considers no significant change in indirect ophthalmoscopy, an additional FA/FP is not mandatory at the baseline visit.

#### **15.1.2.29 Fluorescein angiography and fundus photography combined with wide-field examinations – Section 9.2.2 Baseline visit (Visit 2, Day 1)**

When possible, FA/FP examinations can be combined with wide-field examination and separate fluorescein injection should be avoided per Modification 26 (Section 15.1.1.26).

##### **Old text**

- Ocular assessments (to be conducted in both eyes unless otherwise indicated):
  - Refraction and BCVA using the ETDRS chart (to be performed at each visit)
  - SD-OCT
  - IOP
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - RAPD test
  - FA/FP (the study manual will further specify the standards for FA/FP during the study)

##### **New text**

- Ocular assessments (to be conducted in both eyes unless otherwise indicated):
  - Refraction and BCVA using the ETDRS chart (to be performed at each visit)
  - SD-OCT
  - IOP
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - RAPD test
  - FA/FP (the study manual will further specify the standards for FA/FP during the study). If the investigator considers no significant change in indirect ophthalmoscopy, an additional FA/FP is not mandatory at the baseline visit. Traditional FA/FP examinations can be combined with wide-field examination if possible. A separate fluorescein injection, especially, should be avoided.

#### **15.1.2.30 Assessments at initial visit – Section 9.2.2 Baseline visit (Visit 2, Day 1)**

Specified assessments that should be performed at the initial visit when screening/baseline visits are combined per Modification 28 (Section 15.1.1.28).

**Old text**

- Wide-field FA, at selected study sites
- OCT angiography, at selected study sites
- Full-field ERG, at selected study sites

**New text**

- Wide-field FA, at selected study sites (if screening and baseline visits are combined, assessment should be performed at the initial visit)
- OCT angiography, at selected study sites (if screening and baseline visits are combined, assessment should be performed at the initial visit)
- Full-field ERG, at selected study sites (if screening and baseline visits are combined, assessment should be performed at the initial visit)

**15.1.2.31 Post-treatment safety telephone calls – Section 9.2.2 Baseline visit**

Revised schedule for safety follow-up telephone calls from 3 days after treatment to within 3 days per Modification 30 (Section [15.1.1.30](#)).

**Old text**

- Mandatory safety telephone call 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

**New text**

- Mandatory safety telephone call within 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

**15.1.2.32 Post-treatment safety telephone calls – Section 9.2.3 Initiation phase (2Q4 treatment intervals ( $\pm$  7 days))**

Revised schedule for safety follow-up telephone calls from 3 days after treatment to within 3 days per Modification 30 (Section [15.1.1.30](#)).

**Old text**

- Mandatory safety telephone call 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

**New text**

- Mandatory safety telephone call within 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

**15.1.2.33 Pregnancy testing – Section 9.2.3 Initiation phase (2Q4 treatment intervals  $\pm$  7 days)**

Added that pregnancy testing is mandatory to accommodate local regulatory or institutional requirements per Modification 24 (Section [15.1.1.24](#)).

**Old text**

- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)

**New text**

- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)
- A urine pregnancy test is mandatory prior to injection for women of childbearing potential in all countries where it is required by local regulations

**15.1.2.34 Window for post-baseline study visits – Section 9.2.4.1 Treat and Extend visits**

Clarified that a  $\pm$  7-day window will be allowed for all post-baseline visits per Modification 7 (Section 15.1.1.7).

**Old text**

Treat and Extend visits are scheduled according to an individual subject's T&E schedule.

**New text**

Treat and Extend visits are scheduled according to an individual subject's T&E schedule ( $\pm$  7 days)

**15.1.2.35 Pregnancy testing – Section 9.2.4.1 Treat and Extend visits**

Added that pregnancy testing is mandatory to accommodate local regulatory or institutional requirements per Modification 24 (Section 15.1.1.24).

**Old text**

- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)

**New text**

- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)
- A urine pregnancy test is mandatory prior to injection for women of childbearing potential in all countries where it is required by local regulations

**15.1.2.36 Post-treatment safety telephone calls – Section 9.2.4.1 Treat and Extend visits**

Revised schedule for safety follow-up telephone calls from 3 days after treatment to within 3 days per Modification 30 (Section 15.1.1.30).

**Old text**

- Mandatory safety telephone call 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

**New text**

- Mandatory safety telephone call within 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

**15.1.2.37 Pregnancy testing – Section 9.2.4.2 Week 24 (± 7 days) interim visit**

Added that pregnancy testing is mandatory to accommodate local regulatory or institutional requirements per Modification 24 (Section [15.1.1.24](#))

**Old text**

- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)

**New text**

- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)
- A urine pregnancy test is mandatory prior to injection for women of childbearing potential in all countries where it is required by local regulations

**15.1.2.38 Grammatical correction “pertain” – Section 9.2.4.2 Week 24 (± 7 days)**

Wording changed from “is not a visit pertaining” to “does not pertain” in reference to T&E posology per Modification 31 (Section [15.1.1.31](#)).

**Old text**

The Week 24 visit ~~is not a visit pertaining~~ to the T&E posology.

**New text**

The Week 24 visit does not pertain to the T&E posology

Note: This change also occurs in Section 9.2.4.3 Week 52 (± 7 days) interim visit and Section 9.2.4.4 Week 76 (± 7 days) final study visit. Per template, a terminological change is defined only once, without displaying “Old text” versus “New text” for each appearance.

**15.1.2.39 Post-treatment safety telephone calls – Section 9.2.4.2 Week 24 (± 7 days)**

Revised schedule for safety follow-up telephone calls from 3 days after treatment to within 3 days per Modification 30 (Section [15.1.1.30](#)).

**Old text**

- Mandatory safety telephone call 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

**New text**

- Mandatory safety telephone call within 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

**15.1.2.40 Pregnancy testing – Section 9.2.4.3 Week 52 (± 7 days) interim visit**

Added that pregnancy testing is mandatory for women of childbearing potential at every treatment visit prior to injection if required by local regulations per Modification 24 (Section 15.1.1.24).

**Old text**

- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)

**New text**

- Vital signs (temperature, blood pressure, and heart rate)
- AEs (pre- and post-dose)
- A urine pregnancy test is mandatory prior to injection for women of childbearing potential in all countries where it is required by local regulations

**15.1.2.41 Post-treatment safety telephone calls – Section 9.2.4.3 Week 52 (± 7 days) interim visit**

Revised schedule for safety follow-up telephone calls from 3 days after treatment to within 3 days per Modification 30 (Section 15.1.1.30).

**Old text**

- Mandatory safety telephone call 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

**New text**

- Mandatory safety telephone call within 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

**15.1.2.42 Telephone safety contact with investigator at 30 days post-dose – Section 9.2.4.4 Week 76 (± 7 days) final study visit**

Reworded for clarity that telephone contact is a safety telephone contact with the investigator per Modification 27 (Section 15.1.1.27).

**Old text**

- A mandatory ~~safety patient contact by telephone~~ 30 days after the last administration of study medication is scheduled to ensure ~~no AEs have occurred if the 30-day follow-up period ends after the scheduled Week 76 visit.~~

**New text**

- A mandatory telephone safety contact with the investigator 30 days after the last administration of study medication is scheduled to ensure that the patient has not experienced any AEs.

**15.1.2.43 Telephone safety contact with investigator at 30 days post-dose – Section 9.2.5 Early termination visit**

Reworded for clarity that telephone contact is a safety telephone contact with the investigator per Modification 27 (Section 15.1.1.27).

**Old text**

- A mandatory ~~safety patient contact by telephone~~ 30 days after the last administration of study medication is scheduled to ensure ~~no AEs have occurred if the 30-day follow-up period ends after the scheduled Week 76 visit~~.

**New text**

- A mandatory telephone safety contact with the investigator 30 days after the last administration of study medication is scheduled to ensure that the patient has not experienced any AEs.

**15.1.2.44 Early termination visit – Section 9.2.5 Early termination visit**

Removed sentence describing monitoring interval if subject is withdrawn from the study per Modification 32 (Section 15.1.1.32).

**Old text**

~~In the event that a subject is withdrawn from the study before completing the Week 76 visit, monitoring should be continued with a follow-up visit at a minimum interval of 8 weeks and at all subsequent prescheduled visits (i.e. Weeks 24, 52, and 76). The following assessments should be performed:~~

- Prior and concomitant medications

**New text**

- Prior and concomitant medications

**15.1.2.45 Secondary variable change in retinal perfusion status – Section 9.4.2 Secondary efficacy variables**

Clarified that assessment of secondary variable of change in retinal perfusion status will include screening/baseline combined visit per Modification 3 (Section 15.1.1.3).

**Old text**

- The change in retinal perfusion (FA/FP) status from baseline to Weeks 24, 52, and 76

**New text**

- The change in retinal perfusion (FA/FP) status from screening/baseline to Weeks 24, 52, and 76

#### **15.1.2.46 Exploratory variable perfusion status of retina – Section 9.4.3 Exploratory efficacy variables**

Exploratory variable assessment clarified to include screening/baseline combined visit per Modification 9 (Section 15.1.1.9).

##### **Old text**

Perfusion status of the retina assessed by wide-field at baseline, Week 24, Week 52, and Week 76

##### **New text**

Perfusion status of the retina assessed by wide-field FA at screening/baseline, Weeks 24, 52, and 76

#### **15.1.2.47 Assessments at initial visit – Section 9.4.3 Exploratory efficacy variables**

Table 9-2: Specified assessments that should be performed at the initial visit when screening/baseline visits are combined per Modification 28 (Section 15.1.1.28).

##### **Old text**

EXPLORATORY EFFICACY VARIABLES<sup>a</sup>

<sup>a</sup> At selected sites where instrumentation and technical competence are available.

##### **New text**

EXPLORATORY EFFICACY VARIABLES<sup>a</sup>

<sup>a</sup> At selected sites where instrumentation and technical competence are available. If screening and baseline visits are combined, these assessments should be performed at the initial visit.

#### **15.1.2.48 Fluorescein angiography and fundus photography combined with wide-field examinations – Section 9.4.4.3 Fluorescein angiography and fundus photography**

Clarified that FA/FP examinations can be combined with wide-field examinations to avoid separate fluorescein injection per Modification 26 (Section 15.1.1.26).

##### **Old text**

No related text

##### **New text**

Traditional FA/FP examinations can be combined with wide-field examination if possible. A separate fluorescein injection, especially, should be avoided.

#### **15.1.2.49 Assessments at initial visit – Section 9.4.4.4 Wide-field fluorescein angiography**

Added that assessment should be performed at initial visit if screening and baseline visits are combined per Modification 28 (Section 15.1.1.28).

**Old text**

Wide-field FA of both eyes will be performed at baseline, and of only the study eye at Week 24, Week 52, Week 76, and the early termination visit (and in the fellow eye if there are signs of vein occlusion).

**New text**

Wide-field FA of both eyes will be performed at baseline (or initial visit at combined screening/baseline), and of only the study eye at Weeks 24, 52, and 76, and the early termination visit (and in the fellow eye if there are signs of vein occlusion).

**15.1.2.50 Assessments at initial visit – Section 9.4.4.5 Optical coherence tomography angiography**

Added that assessment should be performed at initial visit if screening and baseline visits are combined per Modification 28 (Section [15.1.1.28](#)).

**Old text**

Optical coherence tomography angiography images of both eyes will be captured at baseline and of only the study eye at Week 24, Week 52, Week 76, and the early termination visit (and in the fellow eye if there are signs of vein occlusion).

**New text**

Optical coherence tomography angiography images of both eyes will be captured at baseline (or initial visit at combined screening/baseline) and of only the study eye at Weeks 24, 52, and 76, and the early termination visit (and in the fellow eye if there are signs of vein occlusion).

**15.1.2.51 Assessments at initial visit – Section 9.4.4.6 Full-field electroretinography**

Added that assessment should be performed at initial visit if screening and baseline visits are combined per Modification 28 (Section [15.1.1.28](#)).

**Old text**

Full-field ERGs will be performed in both eyes at baseline, and only in the study eye at Week 24, Week 52, Week 76, and the early termination visit (and in the fellow eye if there are signs of vein occlusion).

**New text**

Full-field ERGs will be performed in both eyes at baseline (or initial visit at combined screening/baseline) and only in the study eye at Weeks 24, 52, and 76, and the early termination visit (and in the fellow eye if there are signs of vein occlusion).

**15.1.2.52 Pregnancy testing – Section 9.6.3.1 Pregnancy test**

Added that pregnancy testing is mandatory for women of childbearing potential at every treatment visit prior to injection if required by local regulations per Modification 24 (Section [15.1.1.24](#)).



**Old text**

All women of child-bearing potential will have a urine pregnancy test at screening and baseline. If the result of a urine pregnancy test is positive, a serum pregnancy test to confirm results will be done at a local laboratory.

**New text**

All women of child-bearing potential will have a urine pregnancy test at screening. If the result of a urine pregnancy test is positive, a serum pregnancy test to confirm results will be done at a local laboratory. After screening, a urine pregnancy test for women of childbearing potential is mandatory at every treatment visit (prior to injection) in all countries where it is required by local regulations. If required by local regulations, a pregnancy test should be performed for women of childbearing potential at the End of Study visit.

**15.1.2.53 Gonioscopy order of procedure – Section 9.6.3.4.4 Gonioscopy**

Removed wording that gonioscopy is performed after OCT and before FA/FP per Modification 29 (Section 15.1.1.29).

**Old text**

The evaluation will be conducted at screening and at Week 76 and the early termination visit, and may be repeated if needed as determined by the investigator. Gonioscopy will be performed in the study eye only. ~~The examination should be performed after OCT and before FP and FA.~~

**New text**

The evaluation will be conducted at screening and at Week 76 and the early termination visit, and may be repeated if needed as determined by the investigator. Gonioscopy will be performed in the study eye only.

**15.1.2.54 Reference removed - Section 9.6.3.4.5 Relative afferent pupillary defect assessment**

Removed reference to Thompson HS, et al per Modification 33 (Section 15.1.1.33).

**Old text**

Testing for RAPD will be conducted at baseline, Week 24, Week 52, Week 76, and the early termination visit. Testing will be conducted in both eyes ~~as described by Thompson et al~~. A detailed protocol for conducting RAPD testing is provided in the study manual.

**New text**

Testing for RAPD will be conducted at baseline, Weeks 24, 52, and 76, and the early termination visit. Testing will be conducted in both eyes. A detailed protocol for conducting RAPD testing is provided in the study manual.

**15.1.2.55 Window for post-baseline study visits – Section 10.3.1 Variables**

Clarified that a  $\pm 7$ -day window will be allowed for all post-baseline visits per Modification 7 (Section 15.1.1.7).

**Old text**

The visit schedules at Weeks 24, 52, and 76 may deviate by  $\pm 7$  days.

**New text**

A  $\pm 7$ -day window will be allowed for all post-baseline visits.

**15.1.2.56 Secondary variable change in retinal perfusion status –  
Section 10.3.2.2.2 Secondary and exploratory efficacy variables**

Clarified that assessment of secondary variable of change in retinal perfusion status will include screening/baseline combined visit per Modification 3 (Section 15.1.1.3).

**Old text**

- The change in retinal perfusion (FA/FP) status from baseline to Weeks 24, 52, and 76

**New text**

- The change in retinal perfusion (FA/FP) status from screening/baseline to Weeks 24, 52, and 76

**15.1.2.57 Exploratory variable perfusion status of retina – Section 10.3.2.2.2  
Secondary and exploratory efficacy variables**

Exploratory variable assessment clarified to include screening/baseline combined visit per Modification 9 (Section 15.1.1.9).

**Old text**

Perfusion status of the retina assessed by wide-field at baseline, Week 24, Week 52, and Week 76

**New text**

Perfusion status of the retina assessed by wide-field FA at screening/baseline, Weeks 24, 52, and 76

**15.1.2.58 Central reading center for images – Section 13.1 Investigator(s) and  
other study personnel**

Identified that study may be overseen by a Steering Committee per Modification 34 (Section 15.1.1.34).

**Old text**

No related text

**New text****Central reading center for images**

An independent central reading center will evaluate the ophthalmic images defined in Section 9.

### **15.1.2.59 Steering Committee – Section 13.1 Investigator(s) and other study personnel**

Added that the study may be overseen by a Steering Committee per Modification 35 (Section [15.1.1.35](#)).

#### **Old text**

No related text

#### **New text**

#### **External data evaluation bodies**

The sponsor may decide to institute a Steering Committee to guide the trial in all aspects of safety and efficacy and must ensure that all relevant information is provided by investigators. The composition of the team, the functional roles, and responsibilities will be specified in the Charter.

### **15.1.2.60 Adjudication Committee – Section 13.1 Investigator(s) and other study personnel**

Added that an Adjudication Committee will perform additional analysis per Modification 36 (Section [15.1.1.36](#)).

#### **Old text**

No related text

#### **New text**

Finally, an adjudication committee will perform an additional analysis of arterial thrombotic events (ATEs) based on the Antiplatelet Trialists' Collaboration (APTC) endpoint of non-fatal myocardial infarction, non-fatal stroke, and fatal vascular events, including fatal hemorrhages and sudden unexplained death. Details will be described in the Adjudication Committee Charter.

### **15.1.2.61 Reference change – Section 14 Reference list**

Reference list change for SmPC from 24 to 2 per Modification 4 (Section [15.1.1.4](#)).

#### **Old text**

- ~~24. European Medicines Agency. Eylea (Aflibercept) solution for intravitreal injection: summary of product characteristics~~

#### **New text**

2. European Medicines Agency. Eylea (Aflibercept) solution for intravitreal injection: summary of product characteristics

### **15.1.2.62 Study drug vials – Section 16.1 Intravitreal aflibercept injection procedure**

Correction of text in accordance with study drug vials to be supplied per Modification 37 (Section [15.1.1.37](#)).

**Old text**

Intravitreal aflibercept is formulated as a sterile liquid to a final concentration of 40 mg/mL IVT Aflibercept in 5% sucrose, 10 mM sodium phosphate pH 6.2, 0.03% polysorbate 20, and 40 mM NaCl. Intravitreal aflibercept study drug will be supplied by the sponsor in sealed, sterile ~~3-mL~~ vials, each with a “withdrawable” volume of approximately 0.1 mL.

**New text**

Intravitreal aflibercept is formulated as a sterile liquid to a final concentration of 40 mg/mL IVT Aflibercept in 5% sucrose, 10 mM sodium phosphate pH 6.2, 0.03% polysorbate 20, and 40 mM NaCl. Intravitreal aflibercept study drug will be supplied by the sponsor in sealed, sterile 2-mL vials, each with a “withdrawable” volume of approximately 0.1 mL.

**15.1.2.63 Dose preparation – Section 16.1 Intravitreal aflibercept injection procedure**

Removed text stating that dose must be administered within 2 hours of start of dose preparation per Modification 17 (Section [15.1.1.17](#)).

**Old text**

Based on present stability data and the fact that the dosing solution contains no bacteriostatic agents, IVT aflibercept dosing solutions may be kept at room temperature (25°C/77°F) for up to 24 hours. ~~The injection of IVT aflibercept must be completed within 2 hours of the start of dose preparation.~~

**New text**

Based on present stability data and the fact that the dosing solution contains no bacteriostatic agents, IVT aflibercept dosing solutions may be kept at room temperature (25°C/77°F) for up to 24 hours.

**15.1.2.64 Post-treatment safety telephone calls – Appendix 16.1 Intravitreal aflibercept injection procedure**

Revised schedule for safety follow-up telephone calls from 3 days after treatment to within 3 days per Modification 30 (Section [15.1.1.30](#)).

**Old text**

3. A mandatory safety telephone call should be made 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred.

**New text**

3. A mandatory safety telephone call should be made within 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred.

## 16. Appendices – amended

### 16.1 Intravitreal aflibercept injection procedure - amended

#### Study drug dose and volume for administration

Intravitreal aflibercept is formulated as a sterile liquid to a final concentration of 40 mg/mL IVT Aflibercept in 5% sucrose, 10 mM sodium phosphate pH 6.2, 0.03% polysorbate 20, and 40 mM NaCl. Intravitreal aflibercept study drug will be supplied by the sponsor in sealed, sterile 2-mL vials,<sup>73</sup> each with a “withdrawable” volume of approximately 0.1 mL. The volume of injection will be 50 µL (0.05 mL) for the 2 mg dose of IVT aflibercept. The study drug 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 should not be used for IVT injection. The needle should be replaced with a sterile 30-gauge needle for the IVT injection. The contents should be expelled until the plunger is aligned with the line that marks 0.05 mL on the syringe.

When IVT aflibercept vials are removed from the refrigerator, the solution should be visually inspected, and it should have no evidence of turbidity. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Exposure of the material to temperatures outside these limits, except for warming to room temperature prior to administration, is not recommended and may result in loss of activity. Records of actual storage conditions (i.e. temperature log) at the study site must be maintained and must include a record of the dates when the refrigerator was checked, the initials of person checking, and the temperature.

Based on present stability data and the fact that the dosing solution contains no bacteriostatic agents, IVT aflibercept dosing solutions may be kept at room temperature (25°C/77°F) for up to 24 hours.<sup>74</sup>

#### Subject preparation for injection

The physician or designee will prepare the subject for injection.

#### 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. In this protocol, it is recommended that a broad-spectrum topical antibiotic be used as part of the preparation for the IVT injection procedure, and as prophylaxis in the days immediately following the injection.

The use of a topical antibiotic is recommended but is at the discretion of the investigator.

Suggested use:

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<sup>73</sup> Corrected size of vials from 3 mL to 2 mL in accordance with study drug vials to be supplied per Amendment 1, Modification 37 (see Section 15.1.1.37).

<sup>74</sup> Removed text stating that dose must be administered within 2 hours of start of dose preparation per Amendment 1, Modification 17 (see Section 15.1.1.17).



- Instruct the subject to self-administer 1 to 2 drops of the antibiotic to the study eye, 3 times a day, for 3 days before the injection day
- On the injection day, as part of the preparation for injection, instill 1 drop to the eye 1 hour before the injection, and another drop 15 minutes before the injection
- After the injection, instruct the subject to self-administer 1 to 2 drops of the topical antibiotic to the injected eye, 3 times a day, for additional 3 days

### Study drug preparation

***The mandatory sequence of steps required for preparation must be followed for administration of the dose in this clinical trial, as described below.*** This drug administration protocol is based upon the recent guideline published in Retina (23) and current standard of practice.

Preparatory steps:

1. Preparation
  - a. Apply topical anesthetic.
  - b. Apply povidone-iodine to eyelid margins, eyelashes, and conjunctival surface.
  - c. Place 1 or 2 drops of 5% povidone-iodine on the ocular surface at the intended injection site.
  - d. Use sterilized forceps and calipers (speculum) to stabilize the globe and measure the injection site.
  - e. Optional: Inject 0.5 mL of 2% xylocaine without epinephrine subconjunctivally at the intended injection site (the entry site of the needle for the intravitreal injection should be in the inferotemporal quadrant, 3.0 to 3.5 mm from the limbus in aphakic/pseudophakic subjects, and 3.5 to 4.0 mm in the phakic subjects).
  - f. Use sterile fluorescein strips and single use proparacaine bottles for all subjects. Fluoracaine or other combination fluorescein sodium and proparacaine HCl mixtures should NOT be used.
  - g. Drape.
  - h. Apply additional drop of povidone iodine to site of injection.
2. Study drug (VEGF Trap-Eye) administration
  - a. Insert needle at marked injection point.
  - b. Gently inject study drug.
  - c. 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.

Further guidance can be found in The Royal College of Ophthalmologists Intravitreal Injections Procedure Guideline

(<http://www.rcophth.ac.uk/docs/publications/publishedguidelines/IntravitrealInjectionsJuly2006.pdf>).

### Post-injection procedures

1. Indirect ophthalmoscopy in the study eye only.
2. Measure IOP approximately 30 minutes after injection in the study eye only.
3. A mandatory safety telephone call should be made within 3 days<sup>75</sup> after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred.

Additional post-injection management procedures as recommended by the guidelines are as follows:

1. After the injection, instruct the subject to self-administer 1 to 2 drops of a topical antibiotic to the injected eye, 3 times a day, for an additional 3 days.
2. 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.
3. Intraocular pressure

Intraocular pressure may be lowered by pharmaceutical or surgical intervention, if required. If a Tono-Pen is used to check pressure, a clean Tono-Pen condom should be placed on the tip before taking each measurement. If applanation tonometry is used, the applanator tip should be swabbed with alcohol and allowed to dry before using it to measure IOP.

- a. Monitor IOP approximately 30 minutes after each injection.
- b. Check IOP while maintaining a clean field.
- c. Monitor IOP closely until it is 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 subject 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

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<sup>75</sup> Revised schedule for safety follow-up telephone calls from 3 days after treatment to within 3 days per Amendment 1, Modification 30 (see Section 15.1.1.30).



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 all IOP measurements and related treatments in the source document and on the appropriate eCRF page.

### **Discharge**

No special precautions are required before discharge of a subject who has had an uneventful recovery from IVT injection, but subjects 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 with immediately after injection), blurred or decreased vision, and increased ocular sensitivity to light.

- Subjects 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.
- Subjects 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.