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**Managing neovascular age-related macular degeneration (nAMD) over 2 years with a Treat and Extend (T&E) regimen of 2 mg intravitreal (IVT) aflibercept - a randomized, open-label, active-controlled, parallel-group phase IV/IIIb study (ARIES)**

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

- **Original protocol**, Version 1.0, dated 30 Jun 2015
- **Amendment 01** (global amendment described in Section 15.1) forming integrated protocol Version 2.0, dated 02 Feb 2016

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

## 1. Title page

### **Managing neovascular age-related macular degeneration (nAMD) over 2 years with a Treat and Extend (T&E) regimen of 2 mg intravitreal (IVT) aflibercept - a randomized, open-label, active-controlled, parallel-group phase IV/IIIb study (ARIES)**

Managing nAMD with a T&E IVT aflibercept regimen

ARIES

Test drug: BAY86-5321/aflibercept/ VEGF Trap-Eye (Eylea)

Study purpose: To assess whether 2 mg IVT aflibercept administered in an early-start T&E regimen (initiated after the first 8-weekly treatment interval) is non-inferior to 2 mg IVT aflibercept administered in a late-start T&E regimen (initiated at the end of Year 1, per label) in subjects with nAMD.

Clinical study phase: IV/IIIb Date: 02 FEB 2016

Registration: EudraCT: 2014-003132-39 Version no.: 2.0

Sponsor's study no.: BAY86-5321/17508

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

Sponsor's medical expert:



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 clinical study protocol as presented.

Name: PPD 

Role: Medical Affairs Responsible  
(MAR)

Date: \_\_\_\_\_

Signature: \_\_\_\_\_

**Signature of principal investigator**

The signatory agrees to the content of the final 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

<b>Title</b>	Managing neovascular age-related macular degeneration (nAMD) over 2 years with a Treat and Extend (T&E) regimen of 2 mg intravitreal (IVT) aflibercept - a randomized, open-label, active-controlled, parallel-group phase IV/IIIb study (ARIES)
<b>Short title</b>	Managing nAMD with a T&E IVT aflibercept regimen
<b>Acronym</b>	ARIES
<b>Secondary ID</b>	17508
<b>Clinical study phase</b>	IV/IIIb
<b>Study objective(s)</b>	<p><b>Primary objective</b></p> <p>To assess whether 2 mg IVT aflibercept administered in an early-start T&amp;E regimen (initiated after the first 8-weekly treatment interval) is non-inferior to 2 mg IVT aflibercept administered in a late-start T&amp;E regimen (initiated at the end of Year 1, per label) in subjects with nAMD</p> <p><b>Secondary objectives</b></p> <p>To assess the percentage of subjects requiring retreatment with IVT aflibercept less frequently than every 8 weeks (2Q8)</p> <p>To assess the safety and tolerability of IVT aflibercept</p>
<b>Test drug(s)</b>	
<b>Name of active ingredient</b>	Aflibercept (Vascular endothelial growth factor [VEGF] Trap-Eye)
<b>Dose(s)</b>	2 mg (0.05 mL) All subjects during the initiation phase: Three initial monthly doses followed by 1 dose 2Q8 Early-start T&E arm (test group, early treatment individualization): Individualized treatment intervals of between 8 to 16 weeks based on anatomical criteria Late-start T&E arm (per label, control group, treatment individualization after Year 1): Four 8-weekly doses (5 x 2Q8), followed by individualized treatment intervals of between 8 to 16 weeks based on anatomical criteria
<b>Route of administration</b>	IVT
<b>Duration of treatment</b>	104 weeks
<b>Reference drug(s)</b>	None
<b>Background treatment</b>	None

<b>Indication</b>	Neovascular age-related macular degeneration (nAMD)
<b>Diagnosis and main criteria for inclusion /exclusion</b>	Subjects $\geq 50$ years of age with active choroidal neovascularization (CNV) lesions secondary to nAMD
<b>Study design</b>	This is a multicenter, randomized, open-label, active-controlled, parallel-group, Phase IV/IIIb study in subjects with nAMD to assess the non-inferiority of a 2-mg IVT aflibercept T&E dosing regimen initiated after the first 8-weekly treatment interval (3 initial monthly doses followed by 1 dose 2Q8; then treatment individualization) to a 2-mg IVT aflibercept T&E dosing regimen per label (3 initial monthly doses followed by 5 doses 2Q8; treatment individualization after Year 1).

## Methodology

This study comprises a screening phase of up to 3 weeks (Visit 1; -3 weeks to baseline), a baseline visit (Visit 2, Week 0/Day 1), and a treatment phase of 104 weeks.

Only 1 eye will be designated as the study eye. Starting at baseline (Week 0/Day 1), aflibercept 2 mg IVT treatment will be administered to the study eye every 4 weeks (3 initial monthly doses at Weeks 0, 4, and 8). At Week 8, the treatment interval will be extended by 4 weeks (i.e. the next injection will take place at Week 16).

At Week 16, subjects will be stratified based on visual outcomes from baseline to Week 16 (either  $<8$  or  $\geq 8$  letters gain in best-corrected visual acuity [BCVA])<sup>1</sup> and randomized 1:1 into 1 of the following 2 arms:

- In the **early-start T&E arm**, starting at Week 16, subjects will receive treatment in intervals extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met. For subjects who have **no intra-retinal fluid (IRF) and no subretinal fluid (SRF)** at Week 16 (“**completely dry**”), confirmed by the Central Reading Center, the treatment, the treatment interval will be extended by 4 weeks for a total of 12 weeks (i.e. schedule next visit at Week 28). From week 28 onwards, the normal extension algorithm will be applied.
- In the **late-start T&E arm** (per label, control group), subjects will receive treatment every 8 weeks to the end of Year 1 (4 x 2Q8 injections at Weeks 24, 32, 40, and 48). Then in Year 2 (starting from Week 48) the treatment intervals will be extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met.

The anatomical criteria for extending the treatment intervals, based on optical coherence tomography (OCT), are as follows for both study arms:

- Absence of intra-retinal fluid (IRF) and
- Absence of new neovascularization or hemorrhage and
- Subretinal fluid (SRF) not exceeding 50  $\mu\text{m}$  in thickness

If these criteria are not met, the retreatment interval will revert to the last treatment interval in which the disease was inactive.

<sup>1</sup> The threshold for stratification was determined based on the 2Q8 treatment arm from the VIEW 2 study: In this group of 306 subjects, the median BCVA gains at 16 weeks were 8 letters.



<p><b>Methodology</b></p>	<p>After Week 16 (randomization), the treatment intervals will not be less than 8 weeks nor more than 16 weeks with the following exception: If, at any visit after Week 16, the subject has lost 15 or more letters from the best previous BCVA and the actual BCVA is not better than at baseline; or, if the investigator determines, and documents in the eCRF that the subject's condition necessitates more frequent injections than 2Q8, the subject will be considered "injection-intensive". Such subjects will remain in the study, and be treated according to the investigator's best clinical judgment (i.e. the frequency of IVT aflibercept injections is determined by the investigator who is free to subsequently adopt a T&amp;E regimen similar to the per-protocol one, if deemed appropriate for the subject; however, the treatment intervals should not be less than 4 weeks).</p> <p>Due to the per-protocol variability of treatment intervals, subjects may receive their last Year 1 and Year 2 injections at any time between Weeks 42 and 52 (for Year 1) and Weeks 90 and 104 (for Year 2). In case these treatment visits do not occur at Weeks 52 and/or 104 (<math>\pm 1</math> week), the subject will return at Weeks 52 and/or 104 for mandatory visits without treatment.</p> <p>Efficacy will be assessed by the change in BCVA as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score from Week 16 to Week 104 (primary efficacy variable) and by the proportion of subjects maintaining vision (&lt;3 lines loss) at Week 104 compared with baseline (key-secondary efficacy variable). Other secondary measures of efficacy will include changes in BCVA to Week 52 (from baseline and Week 16), the proportion of subjects maintaining or gaining vision, change in central retinal thickness (CRT), and measures related to the number of study drug injections and interval duration. Efficacy will be assessed by BCVA using the ETDRS chart, OCT, and fluorescein angiography (FA)/fundus photography (FP).</p> <p>Assessments of ocular safety will include intraocular pressure (IOP), indirect ophthalmoscopy, and slit lamp biomicroscopy. Overall safety of the subjects will be assessed throughout the study by monitoring ocular and non-ocular adverse events (AEs). All potential arterial thromboembolic events (ATEs) will be adjudicated according to the Antiplatelet Trialists' Collaboration (APTC) endpoints of non-fatal myocardial infarction, non-fatal stroke, and fatal vascular events. Vital signs will be assessed at all study visits.</p>
<p><b>Type of control</b></p>	<p>Different start of the test drug T&amp;E dosing regimen (late-start T&amp;E arm, per label)</p>
<p><b>Number of subjects</b></p>	<p>Approximately 383 screened subjects (254 randomized subjects)</p>
<p><b>Primary variable(s)</b></p>	<p>Change in BCVA as measured by the ETDRS letter score from Week 16 to Week 104</p>
<p><b>Time point/frame of measurement for primary variable(s)</b></p>	<p>Change from Week 16 to Week 104</p>

**Plan for statistical analysis**

Primary variable:

The methodological approach will be the calculation of 2-sided 95% confidence intervals (CI) for the difference in the least squares (LS) means (early-start T&E regimen minus late-start T&E regimen) of the change in ETDRS letter score from Week 16 to Week 104 based on a two-way analysis of covariance (ANCOVA) with the BCVA measure at Week 16 as a covariate and treatment arm and the stratification variable “visual outcomes” as fixed factors (visual outcomes will be determined at Week 16, depending on whether the subjects reached  $<8$  or  $\geq 8$  letters gain in BCVA relative to baseline).

The primary statistical analysis will be performed on the Per-protocol Set (PPS). The early-start T&E regimen will be considered to be non-inferior to the late-start T&E regimen if this analysis is statistically significant, i.e. if the CI of the difference lies entirely above -5 letters, where a positive difference favors the early-start T&E regimen.

Additionally, the analysis will be performed on the Full Analysis Set (FAS) to support the results.

Key secondary efficacy variable (proportion of subjects maintaining vision [ $<3$  lines loss] at Week 104 compared with baseline):

If, and only if, the early-start T&E regimen is statistically proven to be non-inferior to the late-start T&E regimen in the primary efficacy analysis, confirmatory testing will be continued on the PPS to assess the non-inferiority of the early-start T&E regimen to the late start T&E regimen with regard to the key secondary efficacy variable (maintenance of vision).

The methodological approach will be the calculation of 2-sided 95% CIs of the difference between the proportions (early-start T&E regimen minus late-start T&E regimen) of subjects maintaining vision at Week 104, taking the stratification variable “visual outcomes” into account. The early-start T&E regimen will be considered to be non-inferior to the late-start T&E regimen if the CI of the difference lies entirely above -7%, where a positive difference favors the early-start T&E regimen. Additionally, the analysis will be performed on the FAS to support the results,

This hierarchical procedure (a-priori ordered hypotheses) will control for multiplicity in the confirmatory analyses on the PPS.

Analyses on secondary and other efficacy variables will be conducted on the PPS and FAS in a descriptive manner. This may include 95% CIs for treatment differences in an exploratory way.

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## List of abbreviations

2Q8	2 mg aflibercept administered every 8 weeks
AE	Adverse event
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
APTC	Antiplatelet Trialists' Collaboration
ATC	Anatomical Therapeutic Chemical
ATE	Arterial thromboembolic event
BCVA	Best-corrected visual acuity
CI	Confidence interval
CNV	Choroidal neovascularization
CRO	Clinical research organization
CRT	Central retinal thickness
CSR	Clinical study report
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein angiography
FAS	Full Analysis Set
FP	Fundus photography
GCL	Global Clinical Leader
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICF	Informed consent form
ICH	International Conference on Harmonisation
i.e.	That is ( <i>id est</i> )
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IRB	Institutional Review Board
IRF	Intra-retinal fluid
IVT	Intravitreal
IxRS	Interactive voice/web response system
LOCF	Last observation carried forward
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	Neovascular age-related macular degeneration
OCT	Optical coherence tomography
PASS	Power Analysis and Sample Size
PED	Pigment epithelial detachment
PPS	Per-protocol Set
PRN	As needed ( <i>pro re nata</i> )
PRP	Panretinal photocoagulation
RETAIN study	Branch retinal vein occlusion or central retinal vein occlusion
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SID	Subject identification
SOC	System organ class
SRF	Subretinal fluid



StM	Study Manager
SUSAR	Suspected unexpected serious adverse reaction
T&E	Treat and extend
US	United States
V	Visit
VEGF	Vascular endothelial growth factor
VIEW study	VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD
WHODD	World Health Organization Drug Dictionary
Wk	Week

### 3. Introduction - amended

#### Background

Age-related macular degeneration (AMD) is a leading cause of adult blindness in the developed world (1). Age-related macular degeneration has a dry and a wet form, the latter of which accounts for most AMD-related cases of blindness and is referred to as neovascular AMD (nAMD). Severe vision loss from nAMD is caused by a combination of retinal edema and neovascular proliferation. Vascular endothelial growth factor (VEGF), a protein growth factor that both stimulates angiogenesis and increases vascular permeability, is a major pathogenic factor in AMD (2). Anti-VEGF therapy has been shown to provide significant therapeutic benefit to patients suffering from nAMD.

Aflibercept is a potent, specific inhibitor of VEGF with a high affinity for all isoforms of VEGF and placental growth factor. To date, aflibercept has been approved as a treatment for nAMD, diabetic macular edema (DME), and macular edema secondary to branch or<sup>2</sup> central retinal vein occlusion in the United States (US), European Union (EU), Japan, and many<sup>3</sup> other countries; as well as for myopic choroidal neovascularization in the EU, Japan and several other countries; and for diabetic retinopathy in patients with DME in the US.

Further details can be found in the latest available version of the investigator's brochure, which contains comprehensive information on the study drug.

The approved European Union (EU) labeling for Eylea (aflibercept) states:

The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microliters.

Eylea treatment is initiated with 1 injection per month for 3 consecutive doses, followed by 1 injection every 2 months. There is no requirement for monitoring between injections.

After the first 12 months of treatment with Eylea, the treatment interval may be extended based on visual and anatomic outcomes. In this case the schedule for monitoring should be determined by the treating physician and may be more frequent than the schedule of injections.

#### Rationale of the study

The use of anti-VEGF agents for nAMD has become the standard of care. The frequency of dosing for monthly 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 towards individualizing treatment to reduce the burden and minimize reimbursement issues and healthcare costs. The current individualized treatment gaining momentum with practicing physicians is referred to as treat and extend (T&E). In the T&E

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<sup>2</sup> Logical correction of approved indications for aflibercept per Amendment 1 (see Section 15.1.1.1)

<sup>3</sup> Quantity of countries in which aflibercept is approved qualified per Amendment 1 (see Section 15.1.1.2)

dosing paradigm, the subject is injected at every visit and the follow-up examination intervals are incrementally extended according to the response to treatment. The T&E regimen for nAMD was initially described by Spaide in 2007 (3) and applied in several studies since then (4, 5, 6, 7, 8, 9, 10); however, no large-scale studies have examined the use of aflibercept in a T&E regimen in any indication. According to the approved EU label for Eylea, the treatment interval may be extended based on visual and anatomic outcomes after the first 12 months of treatment with Eylea.

Optical coherence tomography (OCT) has been used in clinical practice to guide the detection of macular fluid in order to direct T&E increase, maintenance, or decrease of follow-up intervals. This imaging modality readily permits visualization of anatomic changes common to nAMD such as pigment epithelial detachment (PED), subretinal hyper-reflective material consistent with choroidal neovascularization (CNV), and pathological fluid accumulation (11), as well as anatomic changes.

This study has been designed to assess whether intravitreal (IVT) aflibercept administered in an early-start T&E regimen (initiated after the first 8-weekly treatment interval) is non-inferior to IVT aflibercept administered in a late-start T&E regimen (initiated at the end of Year 1, per the approved EU label for Eylea) in subjects with nAMD. In addition, the percentage of subjects requiring retreatment with IVT aflibercept less frequently than every 8 weeks (2Q8), as well as safety and tolerability, will be assessed.

### **Benefit-risk assessment**

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

The risks of the local IVT application are limited to ocular adverse events (AEs). Due to the low systemic level of aflibercept after IVT injection, 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. In addition, arterial thromboembolic events (ATEs) are AEs potentially related to systemic VEGF inhibition. The risks associated with IVT administration of aflibercept observed in the Phase 3 studies are thought to be similar to those of IVT administration of pegaptanib sodium and ranibizumab.

This study will generate evidence regarding the benefits of early T&E regimen initiation (i.e. initiation in the first year compared to initiation in the second year per the label) in order to provide optimal management of the patient without compromising visual outcomes. Strict extension criteria ensure that the benefit-risk ratio in this study is favorable.

## 4. Study objectives

### Primary objective

To assess whether 2 mg IVT aflibercept administered in an early-start T&E regimen (initiated after the first 8-weekly treatment interval) is non-inferior to 2 mg IVT aflibercept administered in a late-start T&E regimen (initiated at the end of Year 1, per label) in subjects with nAMD.

### Secondary objectives

To assess the percentage of subjects requiring retreatment with IVT aflibercept less frequently than every 8 weeks (2Q8).

To assess the safety and tolerability of IVT aflibercept.

## 5. Study design - amended

### Design overview

This is a multicenter, randomized, open-label, active-controlled, parallel-group, Phase IV/IIIb study in subjects with nAMD to assess the non-inferiority of a 2-mg IVT aflibercept T&E dosing regimen initiated after the first 8-weekly treatment interval (2Q8) to a 2-mg IVT aflibercept T&E dosing regimen per label (treatment individualization after Year 1). In total, approximately 268 subjects in Europe, Canada, and Australia will be treated at baseline. The study duration will be 104 weeks plus the recruitment period.

Subjects must give written informed consent before any data documentation and any study procedure. The study comprises a screening phase of up to 3 weeks (Visit 1; -3 weeks to baseline), a baseline visit (Visit 2, Week 0/Day 1), and a treatment phase of 104 weeks.

Only 1 eye will be designated as the study eye. Starting at baseline (Week 0/Day 1), aflibercept 2 mg IVT treatment will be administered to the study eye every 4 weeks during the initiation phase (3 initial monthly doses at Weeks 0, 4, and 8). At Week 8, the treatment interval will be extended by 4 weeks (i.e. the next injection will take place at Week 16). If subjects require injections at shorter intervals than defined per protocol before or at<sup>4</sup> Week 16, the subjects will not be randomized but withdrawn from the study (see Section 6.3.1).

At Week 16, subjects will be stratified based on visual outcomes from baseline to Week 16 (either <8 or ≥8 letters gain in best-corrected visual acuity [BCVA]) and randomized 1:1 into 1 of the following 2 arms:

- In the **early-start T&E arm** (test group, early treatment individualization), starting at Week 16, subjects will receive treatment in intervals extended by 2 weeks each time

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<sup>4</sup> Point in time for disqualifying subjects for randomization defined more exactly per Amendment 1 (see Section 15.1.1.3)

(up to a maximum of 16 weeks), as long as all anatomical criteria are met.  
(Special case “completely dry”: See below, following the 3 anatomical criteria.)<sup>5</sup>

- In the **late-start T&E arm** (per label, control group, treatment individualization after Year 1), subjects will receive treatment every 8 weeks to the end of Year 1 (4 x 2Q8 injections at Weeks 24, 32, 40, and 48). Then in Year 2 (starting from Week 48) the treatment intervals will be extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met.

The anatomical criteria for extending the treatment intervals for <sup>6</sup>the study eye, based on OCT, are as follows for both study arms:

- Absence of intra-retinal fluid (IRF) and
- Absence of new neovascularization or hemorrhage and
- Subretinal fluid (SRF) not exceeding 50 µm in thickness

For subjects who have **no IRF and no SRF** at Week 16 (“**completely dry**”), confirmed by the Central Reading Center, the treatment interval will be extended by 4 weeks for a total of 12 weeks (i.e. schedule next visit at Week 28). From Week 28 onward, the normal extension algorithm will be applied.<sup>7</sup>

The investigator assesses whether the subject fulfills the anatomical criteria for treatment interval extension and determines the next treatment interval. If the anatomical criteria are not met, the retreatment interval will revert to the last treatment interval in which the disease was inactive.<sup>8</sup> The subject will have all assessments during the proactive extension phase as detailed in Section 9.2.

After Week 16 (randomization), the treatment intervals will not be less than 8 weeks nor more than 16 weeks with the following exception:<sup>9</sup> if, at any visit after Week 16, the subject has lost 15 or more letters from the best previous BCVA and the actual BCVA is not better than at baseline; or, if the investigator determines<sup>10</sup> and documents in the eCRF that the subject’s condition necessitates more frequent injections than 2Q8, the subject will be considered “injection-intensive”.<sup>11</sup> Such subjects will remain in the study, and be treated according to the

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<sup>5</sup> Special case “completely dry” added to the early-start T&E arm per Amendment 1 (see Section 15.1.1.4)

<sup>6</sup> Wording added for more clarity per Amendment 1 (See Section 15.1.1.5)

<sup>7</sup> Special case “completely dry” added to the early-start T&E arm per Amendment 1 (see Section 15.1.1.4)

<sup>8</sup> Option of not extending the treatment interval, even if all anatomical criteria are met, removed per Amendment 1 (see Section 15.1.1.6)

<sup>9</sup> Wording added consistent with synopsis per Amendment 1 (see Section 15.1.1.7)

<sup>10</sup> “Justifies” removed per Amendment 1 (see Section 15.1.1.8)

<sup>11</sup> Sentence split for better readability per Amendment 1 (see Section 15.1.1.9)

investigator's best clinical judgment (i.e. the frequency of IVT aflibercept injections is determined by the investigator who is free to subsequently adopt a T&E regimen similar to the per-protocol one, if deemed appropriate for the subject; however, the treatment intervals should not be less than 4 weeks).

Due to the per-protocol variability of treatment intervals, subjects may receive their last Year 1 and Year 2 injections at any time between Weeks 42 and 52 (for Year 1) and Weeks 90 and 104 (for Year 2). In case these visits do not occur at Weeks 52 and 104 ( $\pm 1$  week), subjects will return at Weeks 52 and/or 104 for mandatory visits, where no study drug is administered, but where examinations are performed from which the primary and secondary outcomes are determined.

On the day of the final visit (Week 104  $\pm 1$  week or early termination) or thereafter, administration of study drug is not allowed. Any subsequent treatment of the underlying disease of a subject is not part of the study and is at the discretion of the subject's physician. Such treatment should only occur after all study relevant assessments have been performed.

The treating investigator must follow up by phone on any AEs that are ongoing or may occur **within 30 days of the last administration of study drug**. Information regarding such events is to be **reported under this protocol** (i.e. not as spontaneous reports).<sup>12</sup>

All ocular assessments are to be conducted in both eyes, unless indicated otherwise. Assessments of ocular safety will include intraocular pressure (IOP), indirect ophthalmoscopy, and slit lamp biomicroscopy; these will be assessed at all study visits. Best-corrected visual acuity and OCT will be conducted at every visit. Mandatory fluorescein angiography (FA)/fundus photography (FP) examinations will only be conducted at screening and at Weeks 52 and 104/early termination. However, the treating investigator may perform FA/FP at other times of the study based on his/her medical judgment and standard of care.

### ***Primary variable***

The primary efficacy variable is the change in BCVA as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score from Week 16 to Week 104.

A list of all efficacy variables including the key-secondary, secondary, and exploratory efficacy variables is provided in Section 9.4. Safety variables are provided in Section 10.3.2.3.

### **Justification of the design**

The use of anti-VEGF agents for nAMD has become the standard of care and the current individualized treatment gaining momentum with practicing physicians is referred to as T&E.

No large-scale studies have examined the use of aflibercept in a T&E regimen in subjects with nAMD. This study in subjects with nAMD aims to assess the non-inferiority of a T&E

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<sup>12</sup> Treatment of underlying disease on the day of the final visit and thereafter; AE reporting after the final study visit (see Section 15.1.1.10)

dosing regimen initiated after the first 8-weekly treatment interval (2Q8) to a T&E dosing regimen per label (treatment individualization after Year 1). The non-inferiority design is adequate to assess the objectives detailed in Section 4.

Open-label setting: Since the T&E dosing regimen in the 2 treatment arms will start at different time points, masking the study would be extremely difficult and would disrupt the intent of a T&E regimen and, thus, was not considered to be a viable option.

For further details on the rationale of the study and the benefit-risk assessment refer to Section 3.

### **End of study**

The end of the study as a whole will be reached as soon as the last visit of the last subject has been reached in all centers in all participating countries (European Union [EU] and non-EU).

### **Primary completion**

The primary completion event for this study is the final study visit at Week 104.

## **6. Study population - amended**

Eligibility for participation in this study will be based on the inclusion/exclusion criteria. An individual subject may only be randomized once.

Subjects eligible for this study must have active CNV lesions secondary to nAMD with foveal involvement.<sup>13</sup> The subjects' eligibility to participate in the study in terms of OCT and FA will be determined initially by the investigator and will have to be confirmed by a central reading center before the first administration of study treatment at the baseline visit.

Only one 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 and least amount of subfoveal scar or geographic atrophy 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.

Ophthalmic eligibility criteria apply to the study eye only unless otherwise specified.

Inclusion and 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. Fluorescein angiography eligibility criteria will be checked against (1) images taken<sup>14</sup> before initiation of treatment with IVT aflibercept and (2) images obtained during the study-screening period.

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<sup>13</sup> Specification of CNV lesions simplified per Amendment 1 (see Section 15.1.1.12)

<sup>14</sup> Time point of nAMD diagnosis removed per Amendment 1 (see Section 15.1.1.11)

## 6.1 Inclusion criteria - amended

1. Written informed consent.
2. Men and women  $\geq 50$  years of age.
3. Active CNV lesions secondary to nAMD with foveal involvement.<sup>15</sup> Subjects with polypoidal choroidal vasculopathy or retinal angiomatous proliferation are eligible to participate in the study, and their condition should be captured in the eCRF.
4. ETDRS BCVA of 73 to 25 letters (20/40 to 20/320 Snellen equivalents) in the study eye.
5. Willing, committed, and able to return for all clinic visits and complete all study-related procedures.
6. Able to read, (or, if unable to read due to visual impairment, be read to verbatim by the person administering the informed consent or a family member) understand and willing to sign the ICF.
7. The area of CNV must occupy at least 50% of the total lesion.
8. Women and men of reproductive potential<sup>16</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.

## 6.2 Exclusion criteria - amended

1. Any prior ocular (in the study eye) or systemic treatment or surgery for nAMD, except dietary supplements or vitamins.
2. Any prior or concomitant therapy with another investigational agent to treat nAMD in the study eye.
3. Prior treatment with anti-VEGF agents as follows:
  - Prior treatment with anti-VEGF therapy in the study eye is not allowed

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<sup>15</sup> Specification of CNV lesions simplified per Amendment 1 (see Section 15.1.1.12)

<sup>16</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.



- Prior treatment with anti-VEGF therapy in the fellow eye with an investigational agent (not approved, e.g. bevacizumab) within the last 3 months before the first dose in the study. Such treatment will also not be allowed during the study. Prior treatment with an approved anti-VEGF therapy in the fellow eye is allowed.
  - Prior systemic anti-VEGF therapy, investigational or approved, within the last 3 months before the first dose in the study, and such treatment will not be allowed during the study.
4. Total lesion size >12 disc areas (30.5 mm<sup>2</sup>, including blood, scars and neovascularization) as assessed by FA in the study eye.
  5. Subretinal hemorrhages that are either 50% or more of the total lesion area, or if the blood is under the fovea and is 1 or more disc areas in size in the study eye. (If the blood is under the fovea, then the fovea must be surrounded by 270 degrees by visible CNV).
  6. Scar or fibrosis making up >25%<sup>17</sup> of the total lesion in the study eye.
  7. Scar, fibrosis, or atrophy involving the center of the fovea in the study eye.
  8. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
  9. History of any vitreous hemorrhage within 4 weeks before screening in the study eye.
  10. Presence of other causes of CNV in the study eye.
  11. Prior vitrectomy in the study eye.
  12. History of retinal detachment or treatment or surgery for retinal detachment in the study eye.
  13. Any history of macular hole of stage 2 and above in the study eye.
  14. Any intraocular surgery, periocular surgery, or cataract surgery within 90 days before Day 1 in the study eye, except lid surgery, which may not have taken place within 1 month of screening, as long as it is unlikely to interfere with the injection.
  15. Only 1 functional eye even if that eye is otherwise eligible for the study.
  16. Prior trabeculectomy or other filtration surgery in the study eye.
  17. Uncontrolled glaucoma (defined as IOP  $\geq$ 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.

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<sup>17</sup> Percentage of scar or fibrosis of total lesions reduced per Amendment 1 (see Section 15.1.1.13)

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 which might interfere with visual acuity, assessment of toxicity or FP.
22. History or clinical evidence of diabetic retinopathy, DME or any retinal vascular disease other than AMD in either eye.
23. Active intraocular, extraocular and periocular inflammation or infection in either eye.
24. Any ocular or periocular infection within the last 2 weeks before screening in either eye.
25. Any history of ocular or periocular Herpes simplex in either eye.
26. Any history of uveitis in either eye.
27. Presence of scleromalacia in either eye.
28. Any concurrent intraocular condition in the study eye that could require either medical or surgical intervention during the 104-week study period.
29. Any concurrent ocular condition in the study eye which, in the opinion of the investigator, could either increase the risk to the subject safety or which otherwise may interfere with evaluation of efficacy or safety.
30. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug.
31. Participation as a subject in any clinical study within 12 weeks before screening.
32. Any systemic or ocular treatment with an investigational agent in the past 3 months before screening.
33. The use of long-acting steroids, either systemically or intraocularly, in the past 6 months before screening.
34. Any history of allergy to the antiseptic used during preparation of the eye for the IVT injection in the investigational site (e.g. povidone iodine or chlorhexidine).
35. Known serious allergy to the fluorescein sodium for injection in angiography.
36. Hypersensitivity to the active substance aflibercept or to any of the excipients.
37. Pregnancy or breastfeeding.
38. 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)
39. Previous assignment to treatment during this study.

## 6.3 Withdrawal of subjects from the study

### 6.3.1 Withdrawal - amended

Note: For this study, premature permanent discontinuation from study medication implies premature discontinuation from study participation.

#### 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.
- Lost-to-follow-up. A subject will be considered lost-to-follow-up if he/she misses 2 consecutive pre-planned study visits without a major reason as agreed upon by the sponsor. All attempts to contact the subject must be documented in the subject's source documents.
- Before or at<sup>18</sup> Week 16 (randomization), subjects require injections at shorter intervals than defined per protocol, based on the anatomical criteria specified in Section 7.1, and on the visual acuity criteria described in Section 9.2.4 for injection-intensive subjects.<sup>19</sup>
- Serious adverse events (SAEs), if sponsor or investigator sees this as medical reason to warrant withdrawal.
- A female subject becomes pregnant.
- At the discretion of the treating physician. The development of conditions which would have prevented a subject's entry into the study according to the selection criteria is no reason per se for withdrawal. However, the withdrawal in such cases remains at the discretion of the treating physician.
- Determination by the investigator that the subject requires alternate treatment for nAMD in the study eye.
- AE (decision to be removed from the study made by either the investigator or the subject). The investigator must notify the sponsor immediately if a subject is withdrawn because of an AE.

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<sup>18</sup> Time point for withdrawing subjects because they need too short injection intervals defined more exactly per Amendment 1 (see Section 15.1.1.14)

<sup>19</sup> Reference to the diagnostic criteria which lead to withdrawal of the subject from the study added per Amendment 1 (see Section 15.1.1.15)

- Decision by the investigator that termination is in the subject's best medical interest or administrative decision for a reason other than an AE.
- Decision by the sponsor to halt the entire study.

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

- If, in the investigator's opinion, 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).
- Decision by the sponsor that termination is in the subject's best medical interest or administrative decision for a reason other than an AE.

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening failure" or "drop-out" as specified below:

### **Screening failure<sup>20</sup>**

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 "drop-out" (see below) is regarded as a "screening failure".

Re-screening of screening failures may be acceptable under the following conditions:

- The subject had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- The reason for the screening failure was a transient event, which subsequently resolved (e.g. decrease of elevated IOP, controlled arterial hypertension) within 30 days.

Under any of the above exceptions, a subject may be re-screened once only. Before a re-screening period is initiated, the subject must sign a new informed consent form. To be eligible, re-screened subjects must meet all selection criteria during the re-screening period.

### **Drop-out**

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

### **General procedures**

In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's medical records. End-of-study/early-termination visit procedures are to be completed at the time of discontinuation and subjects who withdraw should have end-of-study/early

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<sup>20</sup> Screening failure paragraph reworded per Amendment 1 (see Section 15.1.1.16)

termination procedures completed at the time of discontinuation. 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 identification (SID) number is a 9-digit number consisting of a 2-digit country code, a 3-digit center number, and a 4-digit subject number (current subject number within the center).

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

## 7. Treatment(s)

### 7.1 Treatments to be administered - amended

This is an open-label study. The only treatment to be administered to the study eye is 2 mg aflibercept administered as an IVT injection.

Starting at baseline (Week 0/Day 1), after subject eligibility in terms of OCT and FA has been confirmed by a central reading center, IVT aflibercept will be administered to the study eye every 4 weeks during the initiation phase (3 initial monthly doses at Weeks 0, 4, and 8). At Week 8, the treatment interval will be extended by 4 weeks (1 x 2Q8, i.e. the next injection will take place at Week 16).

At Week 16, after stratification based on visual outcomes from baseline to Week 16 (either <8 or ≥8 letters gain in BCVA), subjects will be randomized 1:1 into 1 of the following 2 arms:

- In the **early-start T&E arm** (test group, early treatment individualization), starting at Week 16, subjects will receive treatment in intervals extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met. (Special case “completely dry”: See below, following the 3 anatomical criteria.)<sup>21</sup>
- In the **late-start T&E arm** (per label, control group, treatment individualization after Year 1), subjects will receive treatment every 8 weeks to the end of Year 1 (four 2Q8 injections). Then in Year 2 (starting at Week 48), the treatment intervals will be extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met.

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<sup>21</sup> Special case “completely dry” added to the early-start T&E arm per Amendment 1 (see Section 15.1.1.4)

One-hundred twenty-seven (127) subjects are planned to be randomized into each arm. The treatment duration will be 104 weeks in both arms.

The anatomical criteria, based on OCT, are as follows for both study arms:

- Absence of IRF and
- Absence of new neovascularization or hemorrhage and
- SRF not exceeding 50  $\mu\text{m}$  in thickness

For subjects who have **no IRF and no SRF** at Week 16 (“**completely dry**”), confirmed by the Central Reading Center, the treatment interval will be extended by 4 weeks for a total of 12 weeks (i.e. schedule next visit at Week 28). From Week 28 onward, the normal extension algorithm will be applied.<sup>22</sup>

If these criteria are not met, the retreatment interval will revert to the last treatment interval in which the disease was inactive. In both arms, after Week 8, the treatment intervals will not be less than 8 weeks nor more than 16 weeks.

For further details on determining treatment intervals, see Section 5.

## 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.

The SID number will be recorded on each vial and the SID 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 also entered into the eCRF.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) 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, 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. In accordance with local regulations, each kit may contain one 18-gauge filter needle. Details of the study drug are provided in [Table 7-1](#).

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<sup>22</sup> Special case “completely dry” added to the early-start T&E arm per Amendment 1 (see Section [15.1.1.4](#))

**Table 7-1 Investigational test product**

Name	Dose	Concentration	Volume	Formulation	Composition
BAY 86-5321 /aflibercept/Eylea	2 mg	40 mg/mL	Injected: 0.05 mL	For intravitreal injection	40 mg aflibercept /mL, 5% sucrose, 10 mM sodium phosphate, pH 6.3, 0.03% polysorbate 20, 40 mM sodium chloride, water for injection

### 7.3 Treatment assignment

At Week 16, subjects will be stratified based on visual outcomes from baseline to Week 16 (either  $<8$  or  $\geq 8$  letters gain in BCVA) and randomized to receive treatment under 1 of 2 dosing regimens (see Section 7.1).

The 2 treatment arms will be randomly assigned in a 1:1 ratio by a randomization list generated by the 'Randomization Management' department of Bayer using the Bayer standard randomization tool 'RANDOM'. This randomization list will be uploaded into the interactive voice/web response system (IxRS) of the IxRS supplier to control the correct treatment assignment of each subject.

### 7.4 Dosage and administration

The volume of injection will be 50  $\mu$ L (0.05 mL) for the 2 mg aflibercept dose. 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.

Before administration, the solution for injection needs to be visually inspected. The vial must not be used if particulates, cloudiness, or discoloration are visible.

Before usage, the unopened vial of aflibercept may be stored at room temperature (below 25°C/77°F) for up to 24 hours. After opening the vial, procedures have to take place under aseptic conditions. The aflibercept dosing solutions may be kept at room temperature (25°C) for up to 2 hours (i.e. once the syringe is filled, the injection must be completed within 2 hours of the start of dose preparation).

Aflibercept will be administered via IVT injection to the study eye. For the dosing schedule and planned duration, see Section 7.1. The study drug injection procedure is detailed in Appendix 15.1.2.

### 7.5 Blinding/masking

Not applicable.

## 7.6 Drug logistics and accountability - amended

### Packaging and labeling

For information on packaging and labeling see Section 7.2.

### Storage

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and GMP 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 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.

Aflibercept vials are to be stored at 2°C to 8°C. The drug must not be frozen. Before usage, the unopened aflibercept vial may be stored at room temperature (25°C / 77°F) for up to 24 hours. The temperature in the storage refrigerator has to be measured daily on working days with a min/max 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.

### Accountability

The responsible site personnel will confirm receipt of study drug via 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 <sup>23</sup> 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 approval), or returned to the sponsor or a specified designee for disposal. 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. At the conclusion of the study, photocopies of all drug accountability records will be provided by each site to the sponsor.

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<sup>23</sup> "Partially used" removed per Amendment 1 (see Section 15.1.1.17)



## Supply and return

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.

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

### 7.7 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 before the study, see Section 6.2.

Subjects may not receive any standard or investigational agents for treatment of their AMD in the study eye other than IVT aflibercept as specified in this protocol until they have completed the end of study/early termination visit assessments. This includes medications administered locally (e.g. IVT, by juxtасleral or periorbital routes), as well as those administered systemically with the intent of treating the fellow eye.

If the fellow (non-study) eye has a condition approved to be treated by IVT anti-VEGF, the fellow eye may receive any locally approved non-systemic treatment (Note that fellow-eye IVT aflibercept treatment may be reimbursed<sup>24</sup> in consultation with the sponsor); off-label treatment of the fellow eye with bevacizumab is prohibited. If the fellow eye receives treatment, it is not advised that this occurs on the same day<sup>25</sup> as when the study eye is treated. Even if treated with IVT aflibercept, the fellow eye will not be considered an additional study eye. Subjects who receive treatment for the fellow eye should remain in the study. Safety for the fellow eye, regardless of whether the fellow eye receives treatment, will be monitored at all study visits.

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<sup>24</sup> Study drug must not be used for treatment of the fellow eye (if needed), but may be reimbursed per Amendment 1 (see Section 15.1.1.18)

<sup>25</sup> Time point of the fellow eye treatment reworded per Amendment 1 (see Section 15.1.1.19)

Any previous and concomitant treatments administered to the non-study eye will be recorded in the source documentation and then entered into the “Previous and Concomitant Medications” eCRF screen using the brand name.

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.

All previous and concomitant medications will be coded using an internationally recognized and accepted coding dictionary.

## **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 and standard of care. Such further treatment will occur at the subject’s expense and outside the purview of this study.

## **9. Procedures and variables**

### **9.1 Tabular schedule of evaluations**

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

**Table 9-1 Schedule of Evaluations and Study Procedures - Amended**

Study Phase Treatment Arms	Initiation phase				Random.	Proactive extension phase		All Subjects
	All Subjects					Early-start T&E Arm <sup>a</sup>	Late-start T&E Arm <sup>a</sup>	
Visit <sup>b</sup> /Wk <sup>c</sup>	Screening V1 Wk -3 to 0	Baseline V2 Wk 0 (Day 1)	V3, 4 Wk 4, 8	V5 Wk 16	Visits extended by anatomical criteria <sup>d</sup>	Year 1: Wk 24, 32, 40, 48 Year 2: Visits extended by anatomical criteria <sup>d</sup>	End of study/ Wk 104 or Early termination	
Mandatory visits	Wk -3 to 0	Wk 0	Wk 4, 8	Wk 16	Wk 52 <sup>e</sup>	Wk 52 <sup>e</sup>	Wk 104 <sup>e</sup>	
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Demographic data	X							
Medical/ophthalmic history	X							
Physical examination	X							
Pregnancy test <sup>f</sup>	X	X	(X) <sup>g</sup>	(X) <sup>g</sup>	(X) <sup>g</sup>	(X) <sup>g</sup>	(X) <sup>g</sup>	
BCVA using ETDRS chart <sup>h</sup>	X	X	X	X	X	X	X	
OCT	X	X	X	X	X	X	X	
FA/FP <sup>i</sup>	X				X (Wk 52 only)	X (Wk 52 only)	X	
AEs <sup>k</sup>	X	X	X	X	X	X	X	
Indirect ophthalmoscopy <sup>k</sup>	X	X	X	X	X	X	X	
Slit lamp biomicroscopy	X	X	X	X	X	X	X	
IOP <sup>k</sup>	X	X	X	X	X	X	X	
Vital signs <sup>l</sup>	X	X	X	X	X	X	X	
Prior/concomitant medications	X	X	X	X	X	X	X	
Randomization				X				
Administration of study treatment <sup>m</sup>		X	X	X	X	X	n <sup>26</sup>	
Determination of next treatment interval <sup>p</sup>				X <sup>p</sup>	X	X <sup>q</sup>		
Telephone safety check <sup>f</sup>		X	X	X	X	X	X	

2Q8 = 2 mg aflibercept administered every 8 weeks; AE = adverse event; BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study;  
 FA = fluorescein angiography; FP = fundus photography; IOP = intraocular pressure; IVT = intravitreal; OCT = optical coherence tomography; random. = randomization;  
 T&E = treat and extend; V = visit; Wk = week.

Note: All ocular assessments are to be conducted in both eyes, unless indicated otherwise.

<sup>26</sup> Treatment of underlying disease on the day of the final visit and thereafter; AE reporting after the final study visit per Amendment 1 (see Section 15.1.1.10)

**Table 9–1 Schedule of Evaluations and Study Procedures (continued)**

- a: Three initial monthly IVT aflibercept injections (initiation phase) followed either by one 8-weekly dose (2Q8) in the early-start T&E arm or by five 8-weekly doses (2Q8) in the late-start T&E arm. The treatment interval may then be extended by 2 weeks each time (individualized treatment intervals of between 8 to 16 weeks) based on anatomical outcomes. When/if anatomical outcomes indicate that the disease has re-activated, the treatment interval will revert to the last treatment interval in which the disease was inactive (i.e. no signs of exudation). For details on treatment intervals see Section 5.
- b: Visit numbers refer to the mandatory visits for treatment administration to subjects for the 3 initial monthly doses at Weeks 0, 4, and 8, followed by one 8-weekly dose (2Q8) at the randomization visit.
- c: Visit schedules may deviate by  $\pm 7$  days. Set schedule visits and fixed dosing arms use baseline for the calculation. Flexible visits always use the planned week number of the current visit to calculate the week number of the next visit.<sup>27</sup> The procedures required at each visit have to be complete within 3 days, i.e. split visits are allowed. Additionally, all procedures have to be complete within the 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.
- d: Anatomical criteria: No intraretinal fluid (IRF), no new neovascularization or hemorrhage, and subretinal fluid (SRF) not exceeding 50  $\mu\text{m}$  in thickness.<sup>28</sup> For further details on determining treatment intervals see Section 5.
- e: All subjects will have mandatory visits at Weeks 52 and 104. In case the scheduled retreatment visit does not occur at Weeks 52 and 104 ( $\pm 1$  week), subjects in both treatment arms will still have mandatory visits without treatment at Weeks 52 and 104.
- f: Urine test, for women of child-bearing potential only; a positive result should be confirmed by a serum pregnancy test. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential.
- g: After the first treatment, a urine pregnancy test is mandatory at every treatment visit (prior to injection) in all countries where it is required by local regulations. If required by national /institutional regulations, a pregnancy test should be performed for women of childbearing potential at the end of study visit.
- h: Refraction and BCVA using the ETDRS chart is to be performed at each visit.
- i: Mandatory at screening, Week 52, and Week 104/early termination, but may be performed at other times based on the investigator's medical judgment and standard of care.
- j: The treating investigator must follow up by phone on any AEs that are ongoing or may occur or **within 30 days of the last administration of study drug**. Information regarding such events is to be **reported under this protocol** (i.e. not as a spontaneous report).<sup>29</sup> For any drug-related AE occurring **after 30 days** of the last IVT application of 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.
- k: 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 post-dosing.
- l: Temperature, blood pressure, and heart rate
- m: See Appendix 15.1.2 for an example study drug injection procedure.
- n: On the day of the final visit (Week 104  $\pm 1$  week or early termination) or thereafter, administration of study drug is not allowed. Any subsequent treatment of a subject's underlying disease is not part of the study and is at the discretion of subject's physician. Such treatment should only occur after all study relevant assessments have been performed..<sup>30</sup>
- p: For subjects in the early-start T&E arm only.

(Footnotes continued)

<sup>27</sup> Reference point for visit scheduling reworded per Amendment 1 (see Section 15.1.1.20)

<sup>28</sup> Option of not extending the treatment interval, even if all anatomical criteria are met, removed per Amendment 1 (see Section 15.1.1.6)

<sup>29</sup> Treatment of underlying disease on the day of the final visit and thereafter; AE reporting after the final study visit per Amendment 1 (see Section 15.1.1.10)

<sup>30</sup> Treatment of underlying disease on the day of the final visit and thereafter; AE reporting after the final study visit per Amendment 1 (see Section 15.1.1.10)

(Footnotes continued)

o: Investigator assessment of whether the subject fulfills the anatomical criteria based on OCT for treatment interval extension (see Section 5 for details) and determination of next treatment interval.

q: In Year 2 only (starting from Week 48).

r: A mandatory safety telephone call will be made approximately 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred.

## 9.2 Visit description - amended

Visit schedules may deviate by  $\pm 7$  days. Set schedule visits and fixed dosing arms use baseline for the calculation. Flexible visits always use the planned week number of the current visit to calculate the week number of the next visit.<sup>31</sup> The procedures required at each visit have to be complete within 3 days, i.e. split visits are allowed. Additionally, all procedures have to be complete within the 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.

Note: After the first treatment, a urine pregnancy test is mandatory at every treatment visit (prior to injection) in all countries where it is required by local regulations; a positive result should be confirmed by a serum pregnancy test. If required by national /institutional regulations, a pregnancy test should be performed for women of childbearing potential at the end of study visit.

### 9.2.1 Screening visit (Visit 1, Week -3 to baseline [Week 0])

- Signed ICF (see Section 13.4 for details)
- Allocation of unique SID number (see Section 13.4 for details)
- AEs (see Section 9.6.1 for details)
- Inclusion and exclusion criteria (see Sections 6.1 and 6.2 for details)
- Demographic data (see Section 9.3.1 for details)
- Medical and ophthalmic history (see Section 9.3.2 for details)
- Prior and concomitant medications (see Section 8.1 for details)
- Physical examination (see Section 9.6.3.2 for details)
- Vital signs (temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Urine pregnancy test for women of childbearing potential; a positive result should be confirmed by a serum pregnancy test. Postmenopausal women must be amenorrhic for at least 12 months in order not to be considered of childbearing potential (see Section 9.6.3.1 for details).
- Ocular assessments (see Section 9.7 for details):
  - Refraction and BCVA using the ETDRS chart
  - OCT

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<sup>31</sup> Reference point for visit scheduling redefined per Amendment 1 (see Section 15.1.1.20)

- FP and FA (the study manual will further specify the standards for FA/FP during the study as well as for the historic evaluation of pre-existing images)
- Indirect ophthalmoscopy
- Slit lamp biomicroscopy
- IOP

## 9.2.2 Initiation phase

### 9.2.2.1 Baseline visit (Visit 2, Week 0/Day 1)

- Inclusion and exclusion criteria (see Sections 6.1 and 6.2 for details). This includes a negative urine pregnancy test for women of childbearing potential; a positive result should be confirmed by a serum pregnancy test. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential.
- AEs (pre- and post-dose) (see Section 9.6.1 for details)
- Prior and concomitant medications (see Section 8.1 for details)
- Vital signs (temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Ocular assessment (see Section 9.7 for details) before IVT aflibercept injection:
  - Refraction and BCVA using the ETDRS chart
  - OCT
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - IOP
- IVT injection of study drug (see Section 7.4 for details and Appendix 15.1.2 for an example study drug injection procedure), followed by a 30- to 60-min observation period
  - IOP in the study eye 30 to 60 min following IVT injection
  - Indirect ophthalmoscopy (postdose)
- Mandatory safety telephone call approximately 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

### 9.2.2.2 Visits 3 and 4 (Weeks 4 and 8)

- AEs (pre- and post-dose) (see Section 9.6.1 for details)
- Prior and concomitant medications (see Section 8.1 for details)
- Vital signs (temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)

- Ocular assessment (see Section 9.7 for details) before IVT aflibercept injection:
  - Refraction and BCVA using the ETDRS chart
  - OCT
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - IOP
- IVT injection of study drug (see Section 7.4 for details and Appendix 15.1.2 for an example study drug injection procedure), followed by a 30- to 60-min observation period
  - IOP in the study eye 30 to 60 min following IVT injection
  - Indirect ophthalmoscopy (postdose)
- Mandatory safety telephone call approximately 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

### 9.2.3 Randomization visit (Visit 5, Week 16)

- Stratification based on visual outcomes from baseline to Week 16 (either  $<8$  or  $\geq 8$  letters gain in BCVA) and randomization of subjects via IxRS into the late-start T&E arm or the early-start T&E arm (see Section 7.3 for details)
- AEs (pre- and post-dose) (see Section 9.6.1 for details)
- Prior and concomitant medications (see Section 8.1 for details)
- Vital signs (temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Ocular assessment (see Section 9.7 for details) before IVT aflibercept injection:
  - Refraction and BCVA using the ETDRS chart
  - OCT
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - IOP
- IVT injection of study drug (see Section 7.4 for details and Appendix 15.1.2 for an example study drug injection procedure), followed by a 30- to 60-min observation period
  - IOP in the study eye 30 to 60 min following IVT injection
  - Indirect ophthalmoscopy (postdose)



- For subjects in the early-start T&E arm only: The investigator assesses whether the subject fulfills the anatomical criteria based on OCT (see Section 5 for details) for treatment interval extension and determines the next treatment interval.
- Mandatory safety telephone call approximately 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

#### 9.2.4 Proactive extension phase - amended

In the **early-start T&E arm**, starting at Week 16, subjects will receive treatment in intervals extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met. For subjects who have **no IRF and no SRF** at Week 16 (“**completely dry**”) confirmed by the Central Reading Center, the treatment interval will be extended by 4 weeks for a total of 12 weeks (i.e. schedule next visit at Week 28). From Week 28 onward, the normal extension algorithm will be applied.<sup>32</sup>

In the **late-start T&E arm**, subjects will receive treatment per label, every 8 weeks to the end of Year 1 (2Q8 injections at Weeks 24, 32, 40, 48). Baseline will be used for calculation of fixed visits. Then in Year 2 (starting from Week 48) the treatment intervals will be extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met. Date of the next visit during Year 2 will be calculated based on the actual visit date.<sup>33</sup>

After Week 16 (randomization), the treatment intervals will not be less than 8 weeks nor more than 16 weeks with the following exception: If, at any visit after Week 16, the subject has lost 15 or more letters from the best previous BCVA and the actual BCVA is not better than at baseline; or, if the investigator determines<sup>34</sup> and documents in the eCRF that the subject’s condition necessitates more frequent injections than 2Q8, the subject will be considered “injection-intensive”, remain in the study, and be treated according to the investigator’s best clinical judgment (i.e. the frequency of IVT aflibercept injections is determined by the investigator who is free to subsequently adopt a T&E regimen similar to the per-protocol one, if deemed appropriate for the subject; however, the treatment intervals should not be less than 4 weeks).

All subjects will have a mandatory visit at Week 52. In case a scheduled retreatment visit does not occur at Week 52 ( $\pm 1$  week), subjects in both treatment arms will still have a mandatory visit without treatment at Week 52. With the exception of these mandatory Week-52 and 104 visits, subjects **MUST** receive a treatment when they attend a scheduled study visit (based on their individualized treatment schedule/treatment interval).

##### 9.2.4.1 Treatment visits

The following assessments will be conducted for subjects in both treatment arms:

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<sup>32</sup> Special case “completely dry” added to the early-start T&E arm per Amendment 1 (see Section 15.1.1.4)

<sup>33</sup> Reference point for visit scheduling redefined per Amendment 1 (see Section 15.1.1.20)

<sup>34</sup> “Justifies” removed per Amendment 1 (see Section 15.1.1.8)

- AEs (pre- and post-dose) (see Section 9.6.1 for details)
- Prior and concomitant medications (see Section 8.1 for details)
- Ocular assessment (see Section 9.7 for details) before IVT aflibercept injection:
  - Refraction and BCVA using the ETDRS chart
  - OCT
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - IOP
- Vital signs (temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- IVT injection of study drug (see Section 7.4 for details and Appendix 15.1.2 for an example study drug injection procedure), followed by a 30- to 60-min observation period.
  - IOP in the study eye 30 to 60 min following IVT injection
  - Indirect ophthalmoscopy (post-dose)
- Mandatory safety telephone call approximately 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

At all visits for subjects in the early-start T&E arm and at all Visits in Year 2 (starting from Week 48) for subjects in the late-start T&E arm:

- The investigator assesses whether the subject fulfills the anatomical criteria based on OCT (see Section 5 for details) for treatment interval extension and determines the next treatment interval.

#### **9.2.4.2 Mandatory visit at Week 52**

The following assessments will be conducted for subjects in both treatment arms:

- all assessments as described for the treatment visits in Section 9.2.4.1 will be conducted, except that no study drug will be injected and in consequence, there will be no post-dose assessments of IOP, indirect ophthalmoscopy, AEs, and no safety telephone call (unless the visit coincides with a scheduled treatment visit [ $\pm 1$  week]).
- FP and FA will be conducted (the study manual will further specify the standards for FA/FP during the study as well as for the historic evaluation of pre-existing images).

#### **9.2.5 Final visit (Week 104)/early termination**

All subjects will have a mandatory final visit at Week 104  $\pm 1$  week or early termination. Administration of the study drug is not allowed at this visit. Any subsequent treatment of a subject's underlying disease is not part of the study and is at the discretion of the subject's

physician. Such treatment should only occur after all study- relevant assessments have been performed.

The treating investigator must follow up by phone on any AEs that are ongoing or may occur **within 30 days of the last administration of study drug**. Information regarding such events is to be **reported under this protocol** (i.e. not as spontaneous reports).<sup>35</sup>

If a pregnancy occurs more than 30 days after the last visit or the last IVT injection (whatever is earlier), this report will be processed as a spontaneous report.

- AEs (pre- and post-dose, if applicable) (see Section 9.6.1 for details)
- Prior and concomitant medications (see Section 8.1 for details)
- Vital signs (temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Ocular assessment (see Section 9.7 for details; if an injection is given at this visit, ocular assessments must be completed before administering the injection)
  - Refraction and BCVA using the ETDRS chart
  - OCT
  - FP and FA (the study manual will further specify the standards for FA/FP during the study as well as for the historic evaluation of pre-existing images)
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - IOP
- IVT injection of study drug if the visit coincides with a scheduled treatment visit ( $\pm 1$  week; see Section 7.4 for details and Appendix 15.1.2 for an example study drug injection procedure), followed by a 30- to 60-min observation period.
  - IOP in the study eye 30 to 60 min following IVT injection (as applicable)
  - Indirect ophthalmoscopy (post-dose as applicable)
- Mandatory safety telephone call approximately 3 days after treatment to ensure no signs or symptoms of retinal detachment, endophthalmitis, or other AEs have occurred

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<sup>35</sup> Treatment of underlying disease on the day of the final visit and thereafter; AE reporting after the final study visit per Amendment 1 per Amendment 1 (see Section 15.1.1.10)

### **9.3 Population characteristics**

#### **9.3.1 Demographic**

Subjects will be recruited from men and women  $\geq 50$  years of age. The following demographic parameters will be recorded:

- Gender
- Year of birth
- Weight
- Height
- Race/ethnicity (collection may be restricted per local regulations)

#### **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:

- Not pertaining to the study indication
- Start date before signing of the informed consent
- Considered relevant for the subject's study eligibility

In addition, a complete medical and ophthalmic history will be obtained at screening (Visit 1) to check the in- and exclusion criteria as defined in Sections 6.1 and 6.2, respectively. Detailed instructions on the differentiation between (1) medical history and (2) AEs can be found in Section 9.6.1.1.

### **9.4 Efficacy**

#### **Primary efficacy variable:**

- Change in BCVA as measured by the ETDRS letter score from Week 16 to Week 104

#### **Key-secondary efficacy variable:**

- Proportion of subjects maintaining vision ( $< 3$  lines loss) at Week 104 compared with baseline

#### **Secondary efficacy variables:**

- Change in BCVA as measured by the ETDRS letter score from baseline to Weeks 52 and 104 and from Week 16 to Week 52
- Change in central retinal thickness (CRT) from baseline to Weeks 52 and 104 and from Week 16 to Weeks 52 and 104
- Number of study drug injections from baseline to Weeks 52 and 104
- Duration of last treatment interval

- Proportion of subjects requiring retreatment at 8, 10, 12, 14, and 16 weeks as the last treatment interval
- Proportion of 3-line gainers at Weeks 52 and 104 compared with baseline
- Proportion of subjects maintaining vision (<3 lines loss) at Week 52 compared with baseline

**Exploratory efficacy variables:**

- Change in CNV size and total lesion size from baseline to Weeks 52 and 104
- Proportion of subjects with non-deteriorating OCT morphology (as assessed by the central reading center) at Weeks 52 and 104 compared with baseline
- Proportion of subjects showing no IRF and no SRF at Weeks 8, 16, 52, and 104
- Proportion of subjects showing no IRF and no SRF exceeding 50 µm in thickness at Weeks 52 and 104
- Percentage of subjects requiring retreatment with IVT aflibercept less frequently than every 8 weeks (2Q8)

A complete list of variables to be analyzed for this study will be provided in the statistical analysis plan (SAP).

Note: As each line on the ETDRS chart has 5 letters, subjects maintaining vision (<3 lines loss) are subjects who gain any number of letters, subjects without gain or loss of letters, and subjects who lose less than 15 letters in BCVA; 3-line gainers are subjects who gain at least 15 letters in BCVA.

Ophthalmic procedures to assess efficacy (BCVA using the ETDRS chart, OCT, and FA/FP) are described in Section 9.7.

**9.5 Pharmacokinetics/pharmacodynamics**

Not applicable.

**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**

An 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 which 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)
- 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:

1. The existence of a highly likely alternative explanation, e. g. mechanical bleeding at surgical site.

or

2. 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 treating investigator must follow up by phone on any AEs that are ongoing or may occur **within 30 days of the last administration of study drug**. Information regarding such events is to be **reported under this protocol** (i.e. not as a spontaneous report).<sup>36</sup>

For any drug related<sup>37</sup> AE occurring **after 30 days** of the last application of study drug, the standard procedures that are in place for spontaneous reporting of adverse drug reactions will be followed.<sup>38</sup>

The investigator has to 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.

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 SAEs 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.

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<sup>36</sup> Treatment of underlying disease on the day of the final visit and thereafter; AE reporting after the final study visit per Amendment 1 (see Section 15.1.1.10)

<sup>37</sup> Specification of AE reporting after 30 days of last application of study drug per Amendment 1 (see Section 15.1.1.21)

<sup>38</sup> Treatment of underlying disease on the day of the final visit and thereafter; AE reporting after the final study visit per Amendment 1 (see Section 15.1.1.10)

### **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 adverse events will be collected up until 30 days after the last dose of study drug or the termination visit, whichever is later.

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

### **Notification of the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs)**

Notification of the IECs/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 the EU, the Summary of product characteristics is considered the most appropriate relevant reference safety information. The local label is considered an appropriate reference safety information in other countries.

The expectedness of AEs will be determined by the sponsor according to the 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. If a pregnancy occurs more than 30 days after the last visit or the last IVT injection of study drug<sup>39</sup> (whatever is earlier), this report will be processed as a spontaneous report.

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 until 3 months after birth.

### **9.6.3 Further safety**

#### **9.6.3.1 Laboratory evaluations**

A urine pregnancy test for women of childbearing potential will be performed at screening and baseline. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. After the first treatment, a urine pregnancy test is mandatory at every treatment visit (prior to injection) in all countries where it is required by local regulations. A positive result should be confirmed by a serum pregnancy test. If required by national /institutional regulations, a pregnancy test should be performed for women of childbearing potential at the end of study visit.

The date of each sample obtained and the result will be recorded on the appropriate eCRF page. Pregnancy tests will be performed at a local laboratory. A copy of the results will be filed in the source documentation.

#### **9.6.3.2 Physical examination**

Abnormal physical examination findings are recorded either as medical history or 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 (see Section 9.7).

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<sup>39</sup> "Study drug" added per Amendment 1 (see Section 15.1.1.21)

## 9.7 Other procedures and variables - amended

All potential ATEs will be adjudicated by a masked adjudication committee according to the APTC endpoints of non-fatal myocardial infarction, non-fatal stroke, and fatal vascular events (see also Section 13.1).

All ophthalmic examinations are to be conducted in both eyes, unless indicated otherwise. The following ophthalmic examinations (except for FP/FA) will be conducted at every visit throughout the study. Fundus photography/FA will be conducted at screening (Visit 1), Week 52, and the end of the study (Week 104 visit/early termination visit). The study manual will further specify the standards for FA/FP during the study as well as for the historic evaluation of pre-existing images. The treating investigator may perform additional FA/FP at other times during the 104 weeks of the study based on his/her medical judgment and standard of care.

Care should be taken as much as possible to use the same equipment for all examinations for a certain subject.<sup>40</sup>

### 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).

### 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 AMD. If the fellow eye is not diagnosed with AMD, it will be followed to determine whether AMD 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-tropicamid (or any other mydriatic) applied topically to the eye.

### Intraocular pressure measurement

Intraocular pressure is to be measured using applanation tonometry (Goldmann or Tonopen). The same method of IOP measurement must be used in each subject throughout the study. Pre-injection IOP will be assessed for both the study eye and fellow eye. Assessment of IOP 30 to 60 min following IVT injection will be carried out only in the study eye.

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

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<sup>40</sup> Principle of observation consistency pointed out per Amendment 1 (see Section 15.1.1.23)

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

Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol starting at 4 meters. Visual acuity examiners must be certified to ensure consistent measurement of BCVA, and a refraction will be performed at each visit. Per subject, the same examiner must perform all assessments whenever possible.<sup>41</sup> A detailed protocol for conducting visual acuity testing and refraction can be found in the study manual.

### **Optical coherence tomography**

Retinal and lesion characteristics such as CRT will be evaluated using spectral domain OCT. Images on the study eye and the fellow eye will be captured and assessed by study-site personnel specifically trained and certified for this assessment in order to ensure consistency and quality in image acquisition. All OCT assessments will be electronically archived at the study site as part of the subject's source documentation.

Initially, the OCT images taken at the study site of up to 2 volunteers per site may be assessed by the central reading center to certify the site for central reading. During the study, all OCT images of the study eye will be read by the central reading center as part of this protocol. The subjects' eligibility to participate in the study in terms of OCT will be determined initially by the investigator, but will have to be confirmed by a central reading center before the first administration of study treatment at the baseline visit. Only centrally assessed images for the study eye will be used in the assessment of eligibility for the study and in the analysis of efficacy data. Treatment decisions (i.e. deciding whether a treatment interval can be extended) will be made by the investigator.

A detailed protocol for OCT image acquisition and assessment can be found in the OCT study manual.

### **Fundus photography and fluorescein angiography**

The anatomical state of the retinal vasculature will be evaluated by fundoscopic examination, FP, and FA at screening, Week 52, and Week 104/early termination. The treating investigator may perform additional FA/FP at other times during the study based on his/her medical judgment and standard of care. Photographers must be certified by the reading center to ensure consistency and quality in image acquisition; for certification, images taken at the study site of up to 2 volunteers per site may be assessed by the central reading center. All FA and FP images will be archived at the study site as part of the subject's source documentation.

Fundus photography and FA at the screening visit, Week 52, and Week 104/early termination, and any unscheduled FP or FA imaging will be assessed by the investigator and sent to an independent reading center where images will be read by masked readers. The subjects' eligibility to participate in the study in terms of FA will be determined initially by the investigator, but will have to be confirmed by a central reading center before the first administration of study treatment at the baseline visit. Although FA is performed on both

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<sup>41</sup> Principle of observation consistency pointed out per Amendment 1 (see Section 15.1.1.23)

eyes and both eyes may be evaluated by the investigator, only the study eye will be evaluated by the independent reading center.

The study manual will further specify the standards for FA/FP during the study as well as for the historic evaluation of pre-existing images.

## **9.8 Appropriateness of procedures / measurements**

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

## **10. Statistical methods and determination of sample size**

### **10.1 General considerations**

All statistical issues including definitions and proposed analyses of variables, format and content of tables, and listings and figures will be detailed in the SAP. The SAP will be finalized before enrollment of subjects in the study.

All variables will be analyzed descriptively with appropriate statistical methods: continuous variables by sample statistics (i.e. mean, standard deviation, median, quartiles, and minimum and maximum), and categorical variables by frequency tables (absolute and relative frequencies).

A stratification by visual outcomes at Week 16 is planned, to ensure equal allocation of subgroups, thereby making it easier to interpret the results. Visual outcomes will be determined at Week 16, depending on whether the subjects reached  $<8$  or  $\geq 8$  letters gain in BCVA relative to baseline. The threshold for stratification was determined based on the 2Q8 treatment arm from the VIEW 2 study: In this group of 306 subjects, the median BCVA gains at 16 weeks were 8 letters.

Statistical analysis will be performed using Statistical Analysis System (SAS); the version used will be specified in the SAP.

### **10.2 Analysis sets - amended**

Populations for analysis are defined as follows:

The Full Analysis Set (FAS) will include all randomized subjects who received any study drug and have a BCVA assessment at Week 16 and at least 1 additional post-Week-16 BCVA assessment. The FAS will be analyzed “as randomized”.

The Per-protocol Set (PPS) will include all subjects in the FAS without any major protocol deviation. Major protocol deviations are any violation of in- or exclusion criteria, a treatment duration shorter than 52 weeks, and no BCVA assessment at Week 52 or later. Additionally, injection-intensive subjects who need injections at shorter intervals than 2Q8 between Week 16 and Week 52 will be excluded from the PPS. The PPS will be analyzed “as randomized”.

The Safety Analysis Set (SAF) will include all subjects who received any study drug under this protocol. In the safety analysis, subjects who dropped out after start of treatment before randomization will be described only in ‘total’, since no allocation of such subjects to a treatment arm is possible. Randomized subjects will be analyzed ‘as randomized’.<sup>42</sup>

### **10.3 Variables and planned statistical analyses**

#### **10.3.1 Variables**

For a preliminary list of efficacy and safety variables see Section 9.4 and Section 10.3.2.3, respectively. The complete list and details regarding the derivations of the variables will be provided in the SAP, before enrollment of the first subject.

#### **10.3.2 Statistical and analytical plans**

##### **10.3.2.1 Demography and baseline characteristics - amended**

Demographic and baseline characteristics will be summarized by treatment arm (overall and stratified by “visual outcomes”) and all treatment arms combined for all 3 analysis populations (overall and stratified by visual outcome at Week 16). Medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA) codes and prior and concomitant medications by Anatomical Therapeutic Chemical (ATC) codes (World Health Organization Drug Dictionary [WHODD]).

The treatment arm comparability will be checked for each of the analysis populations (FAS, PPS, SAF). This comparison will be done for age, baseline, and Week 16 BCVA letter score and baseline and Week 16 CRT by a one-way analysis of variance comparing both treatment arms. The test statistics are reliable for variables not normally distributed as well, given the large sample sizes available here. Furthermore, treatment arms will be compared with respect to gender by Chi-squared test.<sup>43</sup>

##### **10.3.2.2 Efficacy analyses**

Details regarding the statistical analyses will be provided in the SAP.

Generally, in non-inferiority studies the most interesting population for efficacy analysis is the PPS, and the FAS should support the results for a valid interpretation. Therefore, the primary efficacy variable will be analyzed for both analysis sets with the PPS as the primary population and the FAS as the supportive one. The key secondary variable will also be analyzed for both analysis sets in the same order.

The other<sup>44</sup> efficacy variables will be analyzed descriptively.

Efficacy data for the treated but non-randomized subjects will be described.

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<sup>42</sup> Paragraph describing the Safety Analysis Set reworded per Amendment 1 (see Section 15.1.1.24)

<sup>43</sup> Paragraph on comparability of treatment arms reworded per Amendment 1 (see Section 15.1.1.25)

<sup>44</sup> “Secondary” deleted per Amendment 1 (see Section 15.1.1.26)



### 10.3.2.2.1 Primary efficacy variable analysis

The primary efficacy variable analysis will be conducted on the PPS and FAS as defined in Section 10.2.

Statistical testing will be conducted to prove the non-inferiority of the early-start T&E regimen to the late-start T&E regimen.

Null hypothesis  $H_0: \mu_1 \leq \mu_2 - D$  versus

Alternative hypothesis  $H_1: \mu_1 > \mu_2 - D$ , where

$D =$  non-inferiority margin

$\mu_i =$  mean change in BCVA as measured by the ETDRS letter score for the study eye from Week 16 to Week 104 in treatment arm  $i$ .

$i =$  1: early-start T&E regimen

2: late-start T&E regimen

The non-inferiority margin  $D$  is set to 5 letters. A non-inferiority margin of 5 letters is consistent with margin used in the “CATT Study” (12).

The methodological approach will be the calculation of 2-sided 95% confidence intervals (CI) for the difference in the least squares (LS) means (early-start T&E regimen minus late-start T&E regimen) of the change in ETDRS letter score from Week 16 to Week 104 based on a two-way analysis of covariance (ANCOVA) with the BCVA measure at Week 16 as a covariate, and treatment arm and the stratification variable “visual outcomes” as fixed factors.

The primary statistical analysis will be performed on the PPS. The early-start T&E regimen will be considered to be non-inferior to the late-start T&E regimen if this analysis is statistically significant, i.e. if the CI of the difference lies entirely above -5 letters, where a positive difference favors the early-start T&E regimen. Additionally, the analysis will be performed on the FAS to support the results.

### 10.3.2.2.2 Secondary efficacy variables

The key secondary efficacy variable analysis will be conducted on the PPS and FAS as defined in Section 10.2.

If, and only if, the early-start T&E regimen is statistically proven to be non-inferior to the late-start T&E regimen in the primary efficacy analysis, confirmatory testing will be continued on the PPS to assess the non-inferiority of the early-start T&E regimen to the late-start T&E regimen with regard to the key secondary efficacy variable (“maintenance of vision”).

Null hypothesis  $H_0: p_1 \leq p_2 - \Delta$  versus

Alternative hypothesis  $H_1: p_1 > p_2 - \Delta$  where

$p_i$  = proportion of subjects maintaining vision at Week 104 of treatment arm  $i$

$\Delta$  = pre-specified non-inferiority margin of 7%<sup>45</sup>.

$i$  = 1: early-start T&E regimen

2: late-start T&E regimen

The methodological approach will be the calculation of 2-sided 95% CIs of the difference between the proportions (early-start T&E regimen minus late-start T&E regimen) of subjects maintaining vision at Week 104 taking the stratification variable “visual outcomes” into account. The early-start T&E regimen will be considered to be non-inferior to the late-start T&E regimen if the CI of the difference lies entirely above -7%, where a positive difference favors the early-start T&E regimen. Additionally, the analysis will be performed on the FAS to support the results.

This hierarchical procedure (a-priori ordered hypotheses) will control for multiplicity in the confirmatory analyses on the PPS.

Analyses on the other secondary efficacy variables will be conducted on the PPS and FAS as defined in Section 10.2 in a descriptive manner, with and without using “visual outcomes” as factor. This may include 95% CIs for treatment differences in an exploratory way.

#### 10.3.2.2.3 Other efficacy variables

The number of injections will be tabulated in both treatment arms. The injection interval data will be tabulated in detail for both treatment arms.

Analyses on exploratory efficacy variables will be conducted on the PPS and FAS in a descriptive manner. This may include 95% CIs for treatment differences in an exploratory way.

#### 10.3.2.3 Safety analysis

The safety analysis will be conducted in the SAF for intervals from baseline to Week 104, baseline to Week 52, and Week 52 to Week 104 by treatment arm.

Treatment-emergent ocular AEs (study eye and fellow eye separately) and non-ocular AEs will be presented by MedDRA preferred term within primary system organ class (SOC) and summarized by treatment arms. Intensity and causal relationship to the investigational product will be analyzed descriptively. Serious AEs, including narratives, will be documented separately.

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<sup>45</sup> The non-inferiority margin of 7% was proposed by the European Medicines Agency (EMA) in their scientific advice of May 2007 during the discussion of the proposed 10% non-inferiority margin in the VIEW studies (EMEA/CHMP/SAWP/310870/2007 pp 22 & 23).

In addition, the incidence of treatment-emergent systemic AEs will be summarized by treatment arm and by treatment arm and concomitant treatment of the fellow eye.

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

### 10.3.3 Missing data/drop outs

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

Missing values regarding the primary and key-secondary efficacy variables will be replaced by “last observation carried forward” (LOCF) using the last available post-baseline values. Last observation carried forward is considered an appropriate method especially in the late phase of the study (i.e. after Week 52), even though untreated nAMD is a progressive disease. Sensitivity analyses (complete cases, maximum-likelihood and/or multiple imputations; see the SAP for details) will be performed to investigate the influence of the missing values.

The handling of other missing or incomplete data will be detailed in the SAP. Methods for avoiding missing values are described in Section 11.4.

## 10.4 Determination of sample size

Based on the assumptions of

- (i) a standard deviation of 13 for the mean change in BCVA from Week 16 to Week 104,
- (ii) a non-inferiority margin of 5 letters,
- (iii) an equal mean change in BCVA from Week 16 to Week 104 in the 2 treatment groups,
- (iv) a power of 80%, and
- (v) a 1-sided  $\alpha$  of 2.5%,

the sample size estimation resulted in 108 evaluable subjects per treatment arm (calculated with Power Analysis and Sample Size (PASS) software, version 11, non-inferiority of 2 means).

With an expected dropout rate of 15% from Week 16 to Week 104, a total of 254 subjects (127 per treatment arm) should be randomized.

With an additional expected dropout rate of 5% until Week 16, approximately 268 subjects have to be treated at baseline.

Approximately 383 subjects have to be screened, assuming that 30% of them will be screening failures.

## 10.5 Planned interim analyses - amended

An interim analysis is planned after all subjects have finished the 52-week visit (or withdrew). No data after visit Week 52 will be used in the interim analysis. Primary and secondary efficacy variables cannot be calculated, as no values from Week 104 will be analyzed. The analysis is only descriptive, no inferential tests will be performed, no decisions on the outcome will be made (e.g. terminating the study or changing the design) and it is planned to publish the descriptive results of this interim analysis. Therefore, no  $\alpha$ -adjustment seems necessary.

Analysis details will be given in the SAP.<sup>46</sup>

## 11. Data handling and quality assurance

### 11.1 Data recording

The data collection tool for this study will be an eCRF; 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, which Bayer/the CRO has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide for use in 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.

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

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<sup>46</sup> Description of interim analysis revised per Amendment 1 (see Section 15.1.1.27)

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; gender; 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. IxRS and 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, e.g. by monitoring in time for completeness (see Section 11.2) and investigators' training, especially to motivate subjects to be compliant with the study protocol. 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 study.

### **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 IEC(s)/IRB(s) 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 (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

It should be noted that the results of the interim analysis cannot lead to a study closure and that no study closure after the interim analysis is possible as no  $\alpha$ -adjustment was planned.

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. IEC(s)/IRB(s); 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**

The Global Clinical Leader (GCL) in cooperation with the Study Manager (StM) will assign the coordinating investigator responsible for signing the final clinical study report (CSR).

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 and the study medical expert are 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.

Key institutions such as the central reading center and external data evaluation bodies are identified in separate documents as well.

#### **Central reading center for images**

An independent central reading center will evaluate the ophthalmic images obtained by OCT and FP/FA (see Section 9.7).

#### **External data evaluation bodies**

The sponsor will institute a steering committee to guide the trial in all aspects of 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.

A masked adjudication committee will perform an additional analysis of ATEs based on the APTC endpoints 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.

### **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 IEC(s)/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 also 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 an integrated subject information sheet and ICF 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 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 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 described 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); 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 will have ample time and opportunity to ask questions.

Only if the subject voluntarily agrees to sign the ICF and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The subject 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 investigator as well as by a signature from the witness.

The ICF and any other written information provided to subjects 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 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 and intends to also publish the results of the interim analysis of the study.

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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5. Gupta OP, Shienbaum G, Patel AH, Fecarotta C, Kaiser RS, Regillo CD. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration clinical and economic impact. *Ophthalmology*. 2010 Nov;117(11):2134-40.
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8. Toalster N, Russell M, Ng P. A 12-month prospective trial of inject and extend regimen for ranibizumab treatment of age-related macular degeneration. *Retina*. 2013 Jul-Aug;33(7):1351-8.
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## 15. Protocol amendments

### Editorial note

In the sections 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 highlighted 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

Correction of typos or omissions are not highlighted.

### 15.1 Amendment 1, dated 25 Jan 2016

#### 15.1.1 Overview of changes to the study

##### 15.1.1.1 Modification 1 – Approved indications for aflibercept

Logical correction of approved indications for aflibercept.

Rationale: Previous version logically incorrect.

The following protocol sections are affected by this modification:

Section 3 Introduction

##### 15.1.1.2 Modification 2 – Countries in which aflibercept is approved

Countries in which aflibercept is approved qualified.

Rationale: Previous version suggested fewer number of countries.

The following protocol sections are affected by this modification:

Section 3 Introduction

### **15.1.1.3 Modification 3 – Time point for disqualifying subjects for randomization**

Time point for disqualifying subjects for randomization defined more exactly.

Rationale: For clarity

The following protocol sections are affected by this modification:

Section 5 Study design

### **15.1.1.4 Modification 4 – Diagnosis “completely dry” at Week 16**

Special case “completely dry” added to the early-start T&E arm.

Rationale: Gain results on subjects responding to the treatment very quickly.

The following protocol sections are affected by this modification:

Section 5 Study design

Section 7.1 Treatments to be administered

Section 9.2.4 Proactive extension phase

### **15.1.1.5 Modification 5 – Anatomical criteria for extending the treatment intervals**

Wording added for more clarity.

Rationale: For clarity.

The following protocol sections are affected by this modification:

Section 5 Study design

### **15.1.1.6 Modification 6 – Option of not extending the treatment interval**

Option of not extending the treatment interval, even if all anatomical criteria are met, removed.

Rationale: On advice of Steering Committee to ensure uniformity of subject management in keeping with protocol and consistency of data.

The following protocol sections are affected by this modification:

Section 5 Study design

[Table 9-1](#) Schedule of Evaluations and Study Procedures

### **15.1.1.7 Modification 7 – Exception for treatment intervals of at least 8 weeks**

Wording added consistent with synopsis.

Rationale: For consistency and clarity.

The following protocol sections are affected by this modification:

Section 5 Study design

#### **15.1.1.8 Modification 8 – Justification for investigator’s treatment decision**

“Justifies” removed.

Rationale: For clarity, to avoid implication that investigator’s treatment decision needs to be approved by an adjudication panel or authority

The following protocol sections are affected by this modification:

Section 5 Study design

Section 9.2.4 Proactive extension phase

#### **15.1.1.9 Modification 9 – Exception for treatment intervals of at least 8 weeks**

Sentence split for better readability.

Rationale: Better readability

The following protocol sections are affected by this modification:

Section 5 Study design

#### **15.1.1.10 Modification 10 – Treatment of underlying disease on the day of the final visit and thereafter; AE reporting after the final study visit**

If subjects need treatment of their underlying disease on the day of the final visit (or thereafter), this is not part of the study and is at the discretion of the subjects’ physician.

AEs ongoing after the final visit or occurring within 30 days of the last injection of study drug must be followed up by phone and be reported under the study protocol (i.e. not as spontaneous reports).

For drug-related AEs occurring after 30 days of the last application of study drug the standard procedures that are in place for spontaneous reporting of adverse drug reactions will be followed.

Rationale: To clarify that the final per protocol study procedures are the pre-injection assessment at week 104 (or early termination). If it is determined, based on these evaluations, that a subject requires an injection at this last visit, this falls outside the scope of the protocol and must therefore be performed according to the physician’s discretion.

Specification of the method of contact for the 30 day safety follow up (i.e. by phone) following the last injection of study drug

The following protocol sections are affected by this modification:

Section 5 Study design

Section 9.1 Tabular schedule of evaluations (Table 9-1 Schedule of Evaluations and Study Procedures

Section 9.2.5 Final visit (Week 104)/early termination

Section 9.6.1.3 Assessments and documentation of adverse events

#### **15.1.1.11 Modification 11 – Reference point for fluorescein angiography eligibility criteria**

Time of nAMD diagnosis removed

Rationale: Checking of FA/FP eligibility criterion against images at time of diagnosis is not required for the trial

The following protocol sections are affected by this modification:

Section 6 Study population

#### **15.1.1.12 Modification 12 – Inclusion criterion 3**

Specification of CNV lesions simplified.

Rationale: As per Steering Committee suggestion; to simplify and broaden the inclusion criterion by removing the quantitative definition of ‘juxtafoveal’

The following protocol sections are affected by this modification:

Section 6 Study population

Section 6.1 Inclusion criteria

#### **15.1.1.13 Modification 13 – Exclusion criterion 6**

Percentage of total lesions for scar or fibrosis reduced.

Rationale: On advice of steering committee to reflect current medical best practice trends.

The following protocol sections are affected by this modification:

Section 6.2 Exclusion criteria

#### **15.1.1.14 Modification 14 – Withdrawal criterion 3**

Time point for withdrawing subjects from the study defined more exactly

Rationale: For clarity

The following protocol sections are affected by this modification:

Section 6.3.1 Withdrawal



### **15.1.1.15 Modification 15 – Withdrawal criterion 3**

Reference to the diagnostic criteria that lead to withdrawal of the subject from the study added

Rationale: For completeness

The following protocol sections are affected by this modification:

Section 6.3.1 Withdrawal

### **15.1.1.16 Modification 16 – Screening failure paragraph**

Text reworded.

Rationale: Updated to be in line with other aflibercept protocols and specify that subject s may only be rescreened once

The following protocol sections are affected by this modification:

Section 6.3.1 Withdrawal

### **15.1.1.17 Modification 17 – Drug accountability**

“Partially used” removed from the types of drugs the study site must account for.

Rationale: For clarity and to ensure that vials are only used a single time.

The following protocol sections are affected by this modification:

Section 7.6 Drug logistics and accountability

### **15.1.1.18 Modification 18 – Fellow eye treatment**

If aflibercept treatment of the fellow eye is warranted, commercial drug should be used.

Rationale: Clarification that the drug will not be supplied by Bayer but may be reimbursed upon consultation with the study team.

The following protocol sections are affected by this modification:

Section 8.1 Prior and concomitant therapy

### **15.1.1.19 Modification 19 – Fellow eye treatment**

Time point of the fellow eye treatment reworded.

Rationale: Less stringent wording, which provides guidance (and protocol preference) but allows for local/ investigator practice patterns

The following protocol sections are affected by this modification:

Section 8.1 Prior and concomitant therapy

#### **15.1.1.20 Modification 20 – Reference point for visit scheduling**

Reference point for visit scheduling reworded in more detail.

Rationale: For clarity and to ensure alignment with structure of database

The following protocol sections are affected by this modification:

Section 9.1 Tabular schedule of evaluations (Table 9-1 Schedule of Evaluations and Study Procedures)

Section 9.2 Visit description

Section 9.2.4 Proactive extension phase

#### **15.1.1.21 Modification 21 – Specification of AE reporting after 30 days of last application of study drug**

Procedure for spontaneous reporting of adverse drug reactions applies for drug related AEs occurring after 30 days of the last administration of the study drug.

Rationale: For clarity and consistency with Footnote j to Table 9-1.

The following protocol sections are affected by this modification:

Section 9.6.1.3 Assessments and documentation of adverse events

#### **15.1.1.22 Modification 22 – Time reference for reporting pregnancy as AE or as spontaneous report**

Addition of “study drug”

Rationale: Clarification that spontaneous reporting applies after dose of study drug.

The following protocol sections are affected by this modification:

Section 9.6.2 Pregnancies

#### **15.1.1.23 Modification 23 – Observation consistency**

Principle of observation consistency pointed out.

Rationale: Good scientific practice.

The following protocol sections are affected by this modification:

Section 9.7 Other procedures and variables

#### **15.1.1.24 Modification 24 – Safety set**

Paragraph describing the Safety Analysis Set reworded.

Rationale: For clarity.

The following protocol sections are affected by this modification:

Section 10.2 Analysis sets

#### **15.1.1.25 Modification 25 – Comparability of treatment arms**

Paragraph on comparability of treatment arms reworded.

Rationale: Harmonization of text between study protocol and statistical plan.

The following protocol sections are affected by this modification:

Section 10.3.2.1 Demography and baseline characteristics

#### **15.1.1.26 Modification 26 – Efficacy variables analyzed descriptively**

“Secondary” deleted.

Rationale: The key secondary variable will be analyzed confirmatively.

The following protocol sections are affected by this modification:

Section 10.3.2.2 Efficacy analyses

#### **15.1.1.27 Modification 27 – Interim analysis**

Description of interim analysis revised.

Rationale: Clarification and harmonization of text between study protocol and statistical plan.

The following protocol sections are affected by this modification:

Section 10.5 Planned interim analyses

#### **15.1.1.28 Modification 28 – Withdrawable volume**

Withdrawable volume corrected

Rationale: Error in original protocol version

The following protocol sections are affected by this modification:

Section 16.1 Aflibercept intravitreal injection procedure

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

Changes to the protocol text are highlighted as specified at the beginning of Section 15

**Approved indications for aflibercept - Section 3 Introduction**

Logical correction of approved indications for aflibercept per Modification 1 (Section 15.1.1.1)

**Old text**

To date, aflibercept has been approved as a treatment for nAMD, diabetic macular edema (DME), and macular edema secondary to branch ~~and~~ central retinal vein occlusion in ...

**New text**

To date, aflibercept has been approved as a treatment for nAMD, diabetic macular edema (DME), and macular edema secondary to branch or central retinal vein occlusion in ...

**Countries in which aflibercept is approved - Section 3 Introduction**

Quantification of countries in which aflibercept is approved qualified per Modification 2 (Section 15.1.1.2)

**Old text**

To date, aflibercept has been approved as a treatment for ... in the United States (US), European Union (EU), Japan and ~~several~~ other countries;

**New text**

To date, aflibercept has been approved as a treatment for ... in the United States (US), European Union (EU), Japan and many other countries;

**Time point for disqualifying subjects for randomization - Section 5 Study design**

Point in time for disqualifying subjects for randomization defined more exactly per Modification 3 (Section 15.1.1.3)

**Old text**

If subjects require injections at shorter intervals than defined per protocol before Week 16, the subjects will not be randomized but withdrawn from the study

**New text**

If subjects require injections at shorter intervals than defined per protocol before or at Week 16, the subjects will not be randomized but withdrawn from the study

## Diagnosis “completely dry”

### Section 5 Study design

#### Section 7.1 Treatments to be administered

#### Section 9.2.4 Proactive extension phase

Special case “completely dry” added to the early-start T&E arm per Modification 4 (Section 15.1.1.4)

#### Old text

In the **early-start T&E arm** (test group, early treatment individualization), starting at Week 16, subjects will receive treatment in intervals extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met.

#### New text

In the **early-start T&E arm** (test group, early treatment individualization), starting at Week 16, subjects will receive treatment in intervals extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met.  
(Special case “completely dry”: See below, following the 3 anatomical criteria.)

#### And definition added:

The anatomical criteria for extending the treatment intervals for the study eye, based on OCT, are as follows for both study arms:

- Absence of intra-retinal fluid (IRF) and
- Absence of new neovascularization or hemorrhage and
- Subretinal fluid (SRF) not exceeding 50 µm in thickness

For subjects who have **no IRF and no SRF** at Week 16 (“**completely dry**”) confirmed by the Central Reading Center, the treatment interval will be extended by 4 weeks for a total of 12 weeks (i.e. schedule next visit at Week 28). From Week 28 onward, the normal extension algorithm will be applied.

#### Anatomical criteria for extending the treatment intervals - Section 5 Study design

Wording added for more clarity per Modification 5 (Section 15.1.1.5)

#### Old text

The anatomical criteria for the study eye, based on OCT, are as follows for both study arms:

**New text**

The anatomical criteria for extending the treatment intervals for the study eye, based on OCT, are as follows for both study arms:

**Option of not extending treatment interval****Section 5 Study design****Section 9.1 Tabular schedule of evaluations (Table 9-1 Schedule of Evaluations and Study Procedures)**

Option of not extending the treatment interval, even if all anatomical criteria are met, removed per Modification 6 (Section 15.1.1.6)

**Old text**

The investigator assesses whether the subject fulfills the anatomical criteria for treatment interval extension and determines the next treatment interval. If the anatomical criteria are not met, the retreatment interval will revert to the last treatment interval in which the disease was inactive. ~~Even if all anatomical criteria are met (including the presence of SRF not exceeding 50 µm in thickness), the investigator will have the option of not extending the treatment interval provided that this decision is adequately medically justified and documented in the electronic case report form (eCRF).~~ The subject will have all assessments during the proactive extension phase as detailed in Section 9.2.

**New text**

The investigator assesses whether the subject fulfills the anatomical criteria for treatment interval extension and determines the next treatment interval. If the anatomical criteria are not met, the retreatment interval will revert to the last treatment interval in which the disease was inactive. The subject will have all assessments during the proactive extension phase as detailed in Section 9.2.

**Exception for treatment intervals of at least 8 weeks - Section 5 Study design**

Wording added consistent with synopsis per Modification 7 (Section 15.1.1.7)

**Old text**

After Week 16 (randomization), the treatment intervals will not be less than 8 weeks nor more than 16 weeks. If, at any visit after Week 16, the subject has ..., the subject will be considered “injection-intensive”.

**New text**

After Week 16 (randomization), the treatment intervals will not be less than 8 weeks nor more than 16 weeks with the following exception: If, at any visit after Week 16, the subject has ..., the subject will be considered “injection-intensive”.

**Justification for investigator’s treatment decision****Section 5 Study design****Section 9.2.4 Proactive extension phase**

“Justifies” removed per Modification 8 (Section [15.1.1.8](#))

**Old text**

After week 16 ... or, if the investigator determines, ~~justifies~~, and documents in the eCRF that the subject’s condition necessitates more frequent injections than 2Q8, the subject will be considered “injection-intensive” (and remain in the study)

**New text**

After week 16 ...or, if the investigator determines and documents in the eCRF that the subject’s condition necessitates more frequent injections than 2Q8, the subject will be considered “injection-intensive” (and remain in the study)

**Exception for treatment intervals of at least 8 weeks – Section 5 Study design**

Sentence split for better readability per Modification 9 (Section [15.1.1.9](#))

**Old text**

After Week 16 (randomization), the treatment intervals will not be less than 8 weeks nor more than 16 weeks with the following exception: If, at any visit after Week 16, the subject has lost 15 or more letters from the best previous BCVA *and* the actual BCVA is not better than at baseline; or, if the investigator determines and documents in the eCRF that the subject’s condition necessitates more frequent injections than 2Q8, the subject will be considered “injection-intensive”, remain in the study, and be treated according to the investigator’s best clinical judgment (i.e. the frequency of IVT aflibercept injections is determined by the investigator who is free to subsequently adopt a T&E regimen similar to the per-protocol one, if deemed appropriate for the subject; however, the treatment intervals should not be less than 4 weeks).

**New text**

After Week 16 (randomization), the treatment intervals will not be less than 8 weeks nor more than 16 weeks with the following exception: If, at any visit after Week 16, the subject has

lost 15 or more letters from the best previous BCVA *and* the actual BCVA is not better than at baseline; or, if the investigator determines and documents in the eCRF that the subject's condition necessitates more frequent injections than 2Q8, the subject will be considered "injection-intensive". Such subjects will remain in the study, and be treated according to the investigator's best clinical judgment (i.e. the frequency of IVT aflibercept injections is determined by the investigator who is free to subsequently adopt a T&E regimen similar to the per-protocol one, if deemed appropriate for the subject; however, the treatment intervals should not be less than 4 weeks).

### **Treatment of underlying disease on the day of the final visit and thereafter; AE reporting after the final study visit**

#### **Section 5 Study design**

#### **Section 9.1 Tabular schedule of evaluations (Table 9-1 Schedule of Evaluations and Study Procedures)**

#### **Section 9.2.5 Final visit (Week 104)/early termination**

#### **Section 9.6.1.3 Assessments and documentation of adverse events**

If a subjects needs an injection of aflibercept on the day of the final visit, commercial drug is to be used. Pertaining AEs are reported as spontaneous AEs. AEs occurring within 30 days of the last injection of study drug must be followed up by phone. – Per Modification 10 (Section 15.1.1.10)

#### **Old text**

~~If a subject receives an injection at Week 104, it is the responsibility of the treating investigator to follow up on any AEs (including ongoing events) that may occur within 30 days following this treatment. Information regarding such events is to be reported under this protocol (i.e. not as spontaneous reports). After Week 104, subjects will return to standard of care.~~

#### **New text**

On the day of the final visit (Week 104 ±1 week or early termination) or thereafter, administration of study drug is not allowed. Any subsequent treatment of the underlying disease of a subject is not part of the study and is at the discretion of the subject's physician. Such treatment should only occur after all study relevant assessments have been performed.

The treating investigator must follow up by phone on any AEs that are ongoing or may occur **within 30 days of the last administration of study drug**. Information regarding such events is to be reported **under this protocol** (i.e. not as spontaneous reports). ~~AEs assigned to the injection of commercial drug at Week 104 are to be reported as spontaneous reports.~~



## Reference point for fluorescein angiography eligibility criteria – Section 6 Study Population

Time of nAMD diagnosis removed per Modification 11 (Section 15.1.1.11)

### Old text

Fluorescein angiography eligibility criteria will be checked against (1) images taken ~~at the time of nAMD diagnosis and~~ before initiation of treatment with IVT aflibercept and (2) images obtained during the study-screening period.

### New text

Fluorescein angiography eligibility criteria will be checked against (1) images taken before initiation of treatment with IVT aflibercept and (2) images obtained during the study-screening period.

## Inclusion criterion 3

Specification of CNV lesions simplified per Modification 12 (Section 15.1.1.12)

### Section 6 Study population

#### Old text

Subjects eligible for this study must have ~~subfoveal~~ CNV secondary to nAMD. ~~“Subfoveal” CNV shall be defined as the presence of subfoveal neovascularization, including juxtafoveal lesions that affect the fovea~~

#### New text

Subjects eligible for this study must have active CNV lesions secondary to nAMD with foveal involvement.

### Section 6.1 Inclusion criteria

#### Old text

3. Active ~~primary subfoveal~~ CNV lesions secondary to nAMD, ~~including juxtafoveal lesions that affect the fovea as evidenced by FA in the study eye~~. Subjects with polypoidal choroidal vasculopathy or retinal angiomatous proliferation are eligible to participate in the study, and their condition should be captured in the eCRF.

#### New text

3. Active CNV lesions secondary to nAMD with foveal involvement. Subjects with polypoidal choroidal vasculopathy or retinal angiomatous proliferation are eligible to participate in the study, and their condition should be captured in the eCRF.

**Exclusion criterion 6 - Section 6.2 Exclusion criteria**

Percentage of total lesions for scar or fibrosis reduced per Modification 13 (Section 15.1.1.13)

**Old text**

6. Scar or fibrosis making up >50% of the total lesion in the study eye.

**New text**

6. Scar or fibrosis making up >25% of the total lesion in the study eye.

**Withdrawal criterion 3 – Section 6.3.1 Withdrawal**

Time point for withdrawing subjects from the study defined more exactly per Modification 14 (Section 15.1.1.14)

Reference to the diagnostic criteria that lead to withdrawal of the subject from the study added per Modification 15 (Section 15.1.1.15)

**Old text**

- Before Week 16 (randomization), subjects require injections at shorter intervals than defined per protocol.

**New text**

- Before or at Week 16 (randomization), subjects require injections at shorter intervals than defined per protocol, based on the anatomical criteria specified in Section 7.1, and on the visual acuity criteria described in Section 9.2.4 for injection-intensive subjects.

**Screening failure paragraph – Section 6.3.1 Withdrawal**

Text reworded per Modification 16 (Section 15.1.1.16)

**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 in-/exclusion criteria preventing the subject’s initial attempt to participate have been changed (via protocol amendment).~~

~~Thus, participation of an initial “screening failure” subject at a later time point even if he/she meets all selection criteria upon re-screening is not acceptable.~~

~~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.~~

#### **New text**

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 as a “screening failure”.

Re-screening of screening failures may be acceptable under the following conditions:

- The subject had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- The reason for the screening failure was a transient event, which subsequently resolved (e.g. decrease of elevated IOP, controlled arterial hypertension) within 30 days.

Under any of the above exceptions, a subject may be re-screened once only. Before a re-screening period is initiated, the subject must sign a new informed consent form. To be eligible, re-screened subjects must meet all selection criteria during the re-screening period.

#### **Drug accountability – Section 7.6 Drug logistics and accountability**

“Partially used” removed from the types of drugs the study site must account for per Modification 17 (Section 15.1.1.17).

#### **Old text**

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.

#### **New text**

The physician or designated medical or pharmacy personnel handling the drug product are responsible for the accountability of all used and unused study drug.

#### **Fellow eye treatment – Section 8.1 Prior and concomitant therapy**

Study drug must not be used for treatment of the fellow eye (if needed), but may be reimbursed per Modification 18 (Section 15.1.1.18)

Time point of the fellow eye treatment reworded per Modification 19 (Section 15.1.1.19)

**Old text**

If the fellow (non-study) eye has a condition approved to be treated by IVT anti-VEGF, the fellow eye may receive any locally approved non-systemic treatment (Note that fellow-eye IVT aflibercept treatment ~~may be supplied under this protocol~~ in consultation with the sponsor); off-label treatment of the fellow eye with bevacizumab is prohibited. If the fellow eye receives treatment, ~~this should not occur at the same visit~~ as when the study eye is treated.

**New text**

If the fellow (non-study) eye has a condition approved to be treated by IVT anti-VEGF, the fellow eye may receive any locally approved non-systemic treatment (Note that fellow-eye IVT aflibercept treatment may be reimbursed in consultation with the sponsor); off-label treatment of the fellow eye with bevacizumab is prohibited. If the fellow eye receives treatment, it is not advised that this occurs on the same day as when the study eye is treated.

**Reference point for visit scheduling****Section 9.1 Tabular schedule of evaluations (Table 9-1 Schedule of Evaluations and Study Procedures)****Section 9.2 Visit description**

Reference point for visit scheduling reworded in more detail per Modification 20 (Section [15.1.1.20](#))

**Old text**

Visit schedules may deviate by  $\pm 7$  days. ~~Scheduled visits should not be altered due to the deviation of the previous visit.~~

**New text**

Visit schedules may deviate by  $\pm 7$  days. Set schedule visits and fixed dosing arms use baseline for the calculation. Flexible visits always use the planned week number of the current visit to calculate the week number of the next visit.

**Section 9.2.4 Proactive extension phase****Old text**

In the **late-start T&E arm**, subjects will receive treatment per label, every 8 weeks to the end of Year 1 (2Q8 injections at Weeks 24, 32, 40, 48). Then in Year 2 (starting from Week 48) the treatment intervals will be extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met.

**New text**

In the **late-start T&E arm**, subjects will receive treatment per label, every 8 weeks to the end of Year 1 (2Q8 injections at Weeks 24, 32, 40, 48). Baseline will be used for calculation of

fixed visits. Then in Year 2 (starting from Week 48) the treatment intervals will be extended by 2 weeks each time (up to a maximum of 16 weeks), as long as all anatomical criteria are met.. Date of the next visit during Year 2 will be calculated based on the actual visit date.

### **Time reference for reporting pregnancy as AE or as spontaneous report – Section 9.6.2 Pregnancies**

Addition of “study drug” per Modification 21 (Section [15.1.1.21](#))

#### **Old text**

If a pregnancy occurs more than 30 days after the last visit or the last IVT injection (whatever is earlier), this report will be processed as a spontaneous report.

#### **New text**

If a pregnancy occurs more than 30 days after the last visit or the last IVT injection of study drug (whatever is earlier), this report will be processed as a spontaneous report.

### **Observation consistency - Section 9.7 Other procedures and variables (medical examinations)**

Principle of observation consistency pointed out per Modification 23 (Section [15.1.1.23](#))

#### **Old text**

All ophthalmic examinations are to be conducted in both eyes, unless indicated otherwise. The following ophthalmic examinations (except for FP/FA) will be conducted at every visit throughout the study. Fundus photography/FA will be conducted at screening (Visit 1), Week 52, and the end of the study (Week 104 visit/early termination visit). The study manual will further specify the standards for FA/FP during the study as well as for the historic evaluation of pre-existing images. The treating investigator may perform additional FA/FP at other times during the 104 weeks of the study based on his/her medical judgment and standard of care.

#### **New text**

All ophthalmic examinations are to be conducted in both eyes, unless indicated otherwise. The following ophthalmic examinations (except for FP/FA) will be conducted at every visit throughout the study. Fundus photography/FA will be conducted at screening (Visit 1), Week 52, and the end of the study (Week 104 visit/early termination visit). The study manual will further specify the standards for FA/FP during the study as well as for the historic evaluation of pre-existing images. The treating investigator may perform additional FA/FP at other times during the 104 weeks of the study based on his/her medical judgment and standard of care.

Care should be taken as much as possible to use the same equipment for all examinations for a certain subject.

**And:**

**Old text**

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

**New text**

Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol starting at 4 meters. Visual acuity examiners must be certified to ensure consistent measurement of BCVA, and a refraction will be performed at each visit. Per subject, the same examiner must perform all assessments whenever possible. A detailed protocol for conducting visual acuity testing and refraction can be found in the study manual.

**Safety set - Section 10.2 Analysis sets**

Paragraph describing the Safety Analysis Set reworded per Modification 24 (Section [15.1.1.24](#))

**Old text**

~~The Safety Analysis Set (SAF) will include all subjects who receive any study drug under this protocol. The SAF will be analyzed “as received”.~~

**New text**

The Safety Analysis Set (SAF) will include all subjects who received any study drug under this protocol. In the safety analysis, subjects who dropped out after start of treatment before randomization will be described only in ‘total’, since no allocation of such subjects to a treatment arm is possible. Randomized subjects will be analyzed ‘as randomized’.

**Comparability of treatment arms – Section 10.3.2.1 Demography and baseline characteristics**

Paragraph on comparability of treatment arms reworded per Modification 25 (Section [15.1.1.25](#))

**Old text**

~~The treatment arm comparability will be checked for each of the analysis populations (FAS, PPS, SAF). This comparison will be done for age, baseline and Week 16 BCVA letter score~~

~~and baseline and Week 16 CRT by a 2-tailed student t-test comparing both treatment arms. The test statistics are reliable for variables not normally distributed as well, given the large sample sizes available here. Furthermore, treatment arms will be compared with respect to gender by Fisher's exact test~~

**New text**

The treatment arm comparability will be checked for each of the analysis populations (FAS, PPS, SAF). This comparison will be done for age, baseline and Week 16 BCVA letter score and baseline and Week 16 CRT by a one-way analysis of variance comparing both treatment arms. The test statistics are reliable for variables not normally distributed as well, given the large sample sizes available here. Furthermore, treatment arms will be compared with respect to gender by Chi-squared test.

**Efficacy variables analyzed descriptively - Section 10.3.2.2 Efficacy analyses**

~~“Secondary”~~ deleted per Modification 26 (Section [15.1.1.26](#))

**Old text**

The other ~~secondary~~ efficacy variables will be analyzed descriptively.

**New text**

The other efficacy variables will be analyzed descriptively.

**Interim analysis - Section 10.5 Planned interim analyses**

Description of interim analysis revised per Modification 27 (Section [15.1.1.27](#))

**Old text**

An interim analysis is planned after all subjects have finished the 52-week visit (or withdrew). ~~Only efficacy~~ data up to Week 52 will be used in the interim analysis. Primary and secondary efficacy variables cannot be calculated, as no values from Week 104 will be analyzed. The analysis is only descriptive, no decisions on the outcome will be made (e.g. terminating the study or changing the design) and it is planned to publish the results of this interim analysis. Therefore, no  $\alpha$ -adjustment seems necessary.

**New text**

An interim analysis is planned after all subjects have finished the 52-week visit (or withdrew). No data after visit Week 52 will be used in the interim analysis. Primary and secondary efficacy variables cannot be calculated, as no values from Week 104 will be analyzed. The analysis is only descriptive, no inferential tests will be performed, no decisions on the outcome will be made (e.g. terminating the study or changing the design) and it is planned to

publish the descriptive results of this interim analysis. Therefore, no  $\alpha$ -adjustment seems necessary.

Analysis details will be given in the SAP.

### **Withdrawable volume - Section 16.1 Aflibercept intravitreal injection procedure**

Withdrawable volume corrected per Modification 28 (Section 15.1.1.28)

#### **Old text**

VEGF Trap-Eye study drug will be supplied by the sponsor in sealed, sterile 2 mL-vials, each with a “withdrawable” volume of approximately ~~0.5~~ mL.

#### **New text**

VEGF Trap-Eye study drug will be supplied by the sponsor in sealed, sterile 2 mL-vials, each with a “withdrawable” volume of approximately 0.1 mL.

## **16. Appendices**

### **16.1 Aflibercept intravitreal injection procedure - amended**

#### **Study drug dose and volume for administration**

VEGF Trap-Eye is formulated as a sterile liquid to a final concentration of 40 mg/mL VEGF Trap-Eye in 5% sucrose, 10 mM sodium phosphate pH 6.3, 0.03% polysorbate 20, and 40 mM NaCl. VEGF Trap-Eye study drug will be supplied by the sponsor in sealed, sterile 2 mL-vials, each with a “withdrawable” volume of approximately 0.1 mL<sup>47</sup>. The volume of injection will be 50  $\mu$ L (0.05 mL) for the 2-mg dose of VEGF Trap-Eye. 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 VEGF Trap-Eye 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.

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<sup>47</sup> Withdrawable volume corrected per Amendment 1 (see Section 15.1.1.28)



Based on present stability data and the fact that the dosing solution contains no bacteriostatic agents, VEGF Trap-Eye dosing solutions may be kept at room temperature (25°C) for up to 2 hours (i.e. once the syringe is filled, the injection of VEGF Trap-Eye must be completed within 2 hours of the start of dose preparation).

### **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 intravitreal 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 intravitreal 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:

- Instruct the subject to self-administer 1-2 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 1-2 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 (13) 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 approximately 3 days 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 1-2 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 tonopen is used to check pressure, a clean tonopen 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 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 to 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.