Document Type:	Study Protocol
Official Title:	An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of 2 mg aflibercept administered by intravitreal injections using two different treatment regimens to subjects with neovascular age-related macular degeneration (nAMD)
NCT Number:	NCT02540954
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An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of 2 mg aflibercept administered by intravitreal injections using two different treatment regimens to subjects with neovascular age-related macular degeneration (nAMD)

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

- **Original protocol**, Version 1.0, dated 26 March 2015
- **Amendment 02** (global amendment described in Section 15.1) forming integrated protocol Version 2.0, dated 10 December 2015

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

1. Title page

Study title

An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of 2 mg aflibercept administered by intravitreal injections using two different treatment regimens to subjects with neovascular age-related macular degeneration (nAMD)

Short title: Efficacy and safety of two different aflibercept regimens in subjects with nAMD

Test drug:	BAY 86-5321 / VEGF Trap-Eye / aflibercept		
Study purpose:	Post-approval commitment		
Clinical study phase:	3b	Date:	10 DEC 2015
Registration:	EudraCT: 2013-000120-33	Version no.:	2.0
Sponsor's study no.:	BAY 86-5321 / 16598		
Sponsor:	**Bayer HealthCare AG, D-51368 Leverkusen, Germany**		

Sponsor's medical expert: PPD, Bayer Pharma AG, Wuppertal, Germany
Phone: PPD
Email: PPD

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

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: Global Clinical Leader

Date: 14-12-2015 Signature: PPD

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 - amended

Title	An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of 2 mg aflibercept administered by intravitreal injections using two different treatment regimens to subjects with neovascular age-related macular degeneration (nAMD)
Short title	Efficacy and safety of two different aflibercept regimens in subjects with nAMD
Clinical study phase	3b
Study objective(s)	Primary objective To compare the efficacy of 2 mg aflibercept administered by two different intravitreal (IVT) treatment regimens to subjects with nAMD Secondary objective To assess the safety and tolerability of aflibercept in this subject population
Test drug(s)	
Name of active ingredient	Intravitreal aflibercept injection (IAI)/ BAY 86-5321
Dose(s) - amended	Test group: 2 mg with flexible injection intervals (≥ 8 weeks) (extended-dosing regimen) Control group: 2 mg with fixed injection intervals (8 weeks) (2Q8)[1]
Route of administration	Intravitreal (IVT)
Duration of treatment	72 weeks in the 2Q8 and up to 76 weeks in the extended-dosing group
Reference drug(s)	Not applicable
Indication	Neovascular age-related macular degeneration (nAMD)
Diagnosis and main criteria for inclusion / exclusion - amended	**First set** of inclusion criteria: The following criteria must have been met at the initial start of aflibercept treatment (i.e. start of aflibercept treatment before this study): • Subject had primary subfoveal choroidal neovascularization (CNV) lesions secondary to nAMD, including juxtafoveal lesions that affect the fovea, as evidenced by fluorescein angiography (FA) of the study eye within 4 weeks before the initiation of aflibercept treatment.[2,3] • The area of CNV occupied at least 50% of the total lesion within 4 weeks before the initiation of aflibercept treatment.[3]

1 Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline per Amendment 2

2 Clarification of inclusion criteria per Amendment 2

3 Extension of the time period per Amendment 2

- Documented best-corrected visual acuity (BCVA) was 20/40 to 20/320 (comparable to a letter score of 73 to 25) in the study eye at the initiation of treatment (the initial BCVA of the study eye before treatment initiation must be documented as Snellen equivalent in the electronic case report form [eCRF]).4

Second set of inclusion criteria:

Criteria that must be met at the time of screening include the following (incomplete list):

- Men and women ≥ 51 years of age
- The subject's history of aflibercept treatment meets ALL of the following:
  a) Treatment in the study eye was initiated with three monthly (-1 week/+2 weeks) doses of 2 mg aflibercept and improvements of visual and anatomic outcomes were observed
  b) Following the above initiation phase, the intervals between treatments were between 6 weeks and 12 weeks (one exception will be allowed)
  c) The interval between the last two pre-study injections was ≥8 weeks, and visual and anatomic outcomes have been stable over this interval.
  d) The subject received the last IVT injection of aflibercept in the study eye 2 months (±10 days) before the first treatment in this study[5]
  e) Total prior treatment duration with aflibercept (i.e. from first treatment to randomization into this study) was ≥12 months

4 Clarifications of inclusion criteria and removal of reference to study manual per Amendment 2

5 Clarifications in the first and second set of inclusion criteria per Amendment 2

First set of exclusion criteria:

A subject who has met any of the following criteria at the initial start of aflibercept treatment (i.e. start of aflibercept treatment before this study) will be excluded from this study.

- Any prior or concomitant therapy with an investigational or approved agent to treat neovascular AMD in the study eye.
- Total lesion size >12 disc areas (30.5 mm^2, including blood, scars and neovascularization) as assessed by FA in the study eye
- Subretinal hemorrhage that was:
  a) 50% or more of the total lesion area, or
  b) if the blood was under the fovea, and
  c) the blood under the fovea was 1 or more disc areas in size in the study eye.
- Scar or fibrosis making up more than 50% of the total lesion in the study eye.
- Scar, fibrosis, or atrophy involving the center of the fovea in the study eye.
- Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
- Causes of CNV other than AMD in the study eye.

Second set of exclusion criteria:

Criteria leading to exclusion if met at the time of screening include the following (incomplete list):

- Subjects who currently meet any of the first set of exclusion criteria with the exception of prior treatment with aflibercept
- Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD, except dietary supplements, vitamins and IVT injections of aflibercept, during the time (i.e. at least 12 months) between initiation of aflibercept treatment and randomization into this study
- Any prior treatment with anti-VEGF therapy in the study eye, with the exception of IVT injections of aflibercept, during the time (i.e. at least 12 months) between initiation of aflibercept treatment and randomization into this study
- Prior systemic anti-VEGF therapy, investigational or approved, within the last 15 months prior to randomization

Study design -amended	This is a randomized, 2-arm, active-controlled, parallel-group, open-label, multicenter, Phase-3b study to assess the non-inferiority of an extended-dosing regimen of aflibercept to a 2Q8 fixed dosing regimen in subjects with nAMD who have completed 1 year of treatment with marketed aflibercept according to the approved European Union (EU) drug label. In order to be eligible for the study, the subject's first year of aflibercept treatment must have (i) been initiated with three monthly (-1 week/+2 weeks) doses; and (ii) included treatment intervals between 6 weeks and 12 weeks (one exception will be allowed). This study comprises a screening period of up to 66 days.[6] Following screening, eligible subjects will be randomized (1:1) to one of two parallel treatment arms. In both arms, aflibercept will be injected IVT at a dose of 2 mg per injection. The treatment arms differ in dosing intervals: **Extended dosing**: <u>Flexible dosing intervals</u> ≥8 weeks (no upper limit) based on visual and anatomic outcomes as judged by the investigator. When/if visual and 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 were observed). **2Q8**: <u>Fixed dosing intervals</u> 8 weeks[7] - modification of the treatment interval is not allowed. For each treatment group, the time window for all post-baseline visits is ± 3 days relative to baseline.[7] Subjects in both treatment groups will receive the first study treatment on Day 1. The treatment period is 72 weeks (in the 2Q8 group) with a final study visit at Week 76.[8] The last possible study drug injection in the extended-dosing group can be given at Week 76 (i.e. the end of the study) after completion of all protocol-specified assessments.[9] After Week 76, subjects should be returned to standard of care. The primary efficacy variable is the change in BCVA (as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score starting at 4 meters) from baseline to Week 52.

6 Clarification of the period durations per Amendment 2

7 Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline per Amendment 2

8 Clarification of the period durations per Amendment 2

9 If an extended-dosing subject receives an injection at Week 76, it is the responsibility of the treating investigator to follow-up on any adverse events (including ongoing events) that may occur within 4 weeks following this treatment. Information regarding such events is to be reported under this protocol (i.e. not as spontaneous reports).

Methodology	This study will be conducted as a 2-arm, open-label study. **Efficacy** will be assessed by the change in ETDRS BCVA letter score from study baseline. BCVA will be evaluated at every study visit. Other measures of efficacy will include changes from baseline in central retinal thickness (CRT) as measured by optical coherence tomography (OCT) at each visit, and changes from baseline in quality of life as assessed by the National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) at baseline, Week 52 and Week 76. Assessments of **ocular safety** will include intraocular pressure (IOP), indirect ophthalmoscopy, and slit lamp biomicroscopy at all study visits. Under this protocol, mandated FA/FP examinations will be conducted during screening and at Weeks 52 and 76 only. However, the treating investigator may perform FA/FP at other times during the study based on his/her medical judgment and standard of care. **Overall safety** of the subjects will be assessed throughout the study by monitoring ophthalmic and systemic adverse events (AEs). All potential arterial thrombotic 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 and laboratory tests (hematology parameters, blood chemistry parameters, and parameters of urinalysis) will be performed at study baseline and at Week 76 only.
Type of control	Different dosing schedules of the test drug
Number of subjects	330 (165 per treatment group)
Primary and secondary variable(s)	**Primary efficacy variable** – Change in ETDRS BCVA letter score for the study eye from baseline to Week 52 **Key secondary efficacy variable** – Proportion of subjects maintaining vision (i.e. loss of <15 letters) in the study eye at Week 52 **Secondary efficacy variables** – Proportion of subjects who gained ≥5 letters from baseline to Week 52 – Mean change in central retinal thickness (CRT) in the study eye from baseline to Week 52 – Mean change in CNV area in the study eye from baseline to Week 52 – Proportion of subjects who lost ≥30 letters from baseline to Week 52 – Mean change from baseline to Week 52 in total score for NEI VFQ-25
Time point/frame of measurement for primary variable(s)	BCVA will be measured at each visit up to the final visit.

Plan for statistical analysis	The **primary efficacy variable analysis** will be conducted on the full analysis set (FAS). The FAS is defined as all randomized subjects who received any study drug *and* have a baseline BCVA assessment *and* at least one post-baseline BCVA assessment. Statistical testing will be conducted to prove the non-inferiority of the extended-dosing regimen to the 2Q8 fixed-dosing regimen. Null hypothesis H_0: $\mu 1 \leq \mu 2\text{-}D$ versus Alternative hypothesis H_1: $\mu 1 > \mu 2\text{-}D$, where D = non-inferiority margin μi = mean change in BCVA letter score for the study eye from baseline to Week 52 in treatment group i. i = 1: extended-dosing regimen 2: fixed-dosing regimen The non-inferiority margin is 5 letters. The methodological approach will be the calculation of two-sided 95% confidence intervals for the difference in the least squares means (extended-dosing group minus 2Q8 group) of the change in ETDRS letter score from study baseline to Week 52 based on a one-way analysis of covariance (ANCOVA) with baseline measure as a covariate and treatment group as a fixed factor (last observation carried forward [LOCF] will be used for missing values at Week 52[10]). The extended-dosing regimen will be considered to be non-inferior to the fixed 2Q8 regimen if the confidence interval of the difference lies entirely above -5 letters, where a positive difference favors extended dosing. A non-inferiority margin of 5 letters is consistent with the margin used in the "CATT Study" (Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration. N Eng J Med 2011; 365:1897-1908).

10 LOCF is considered an appropriate method for replacement of missing values in the primary and secondary efficacy analyses in the late phase of the study (i.e. carrying forward the last measurement taken between Week 36 to Week 48 if the Week-52 measurement is missing), even though nAMD is a progressive disease.

If, and only if, the extended-dosing regimen is statistically proven to be non-inferior to the fixed 2Q8 regimen in the primary efficacy analysis, confirmatory testing will be continued to assess the non-inferiority of extended dosing to fixed 2Q8 with regard to the **key secondary efficacy variable** (maintenance of vision) in the full analysis set (FAS; with LOCF for missing Week-52 ETDRS letter score).

Null hypothesis H_0: $p1 \leq p2-\Delta$ versus

Alternative hypothesis H_1: $p1 > p2-\Delta$, where

pi = proportion of subjects maintaining vision at Week 52 of treatment group i

Δ = pre-specified non-inferiority margin of 7%.[11]

i = 1: extended-dosing regimen
2: fixed-dosing regimen

The methodological approach will be the calculation of two-sided 95% confidence intervals using normal approximation of the difference between the proportions (extended-dosing group minus 2Q8 group) of subjects maintaining vision. The extended-dosing regimen will be considered to be non-inferior to the fixed 2Q8 regimen if the confidence interval of the difference lies entirely above -7%, where a positive difference favors extended dosing. This conditional sequence of statistical hypotheses (a-priori ordered hypotheses) will control for multiplicity in the confirmatory analyses.

As sensitivity analyses, the primary efficacy and key secondary efficacy analyses will be repeated on the per-protocol set (PPS). The PPS is defined as all randomized subjects who receive any study drug and have a BCVA assessment at study baseline and have at least one BCVA assessment at Week 36 or later, and do not have a major protocol deviation.

The other secondary efficacy variables as well as the exploratory efficacy variables will be analyzed in a descriptive manner. This may include 95% confidence intervals for treatment differences in an exploratory way.

Details regarding the statistical analyses will be provided in the Statistical Analysis Plan (SAP).

11 The non-inferiority margin of 7% was proposed by the 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 pages 22 and 23).

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List of abbreviations

2Q8	2 mg aflibercept administered every 8 weeks
AE	adverse event
ALT	alanine aminotransferase
AMD	age-related macular degeneration
ANCOVA	analysis of covariance
APTC	Antiplatelet Trialists' Collaboration
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATE	arterial thrombotic event
BCVA	best corrected visual acuity
BL	Baseline
BRVO	branch retinal vein occlusion
BUN	blood urea nitrogen
CIE	Conference on computability in Europe
CNV	choroidal neovascularization
CRF	case record form
CRO	contract research organization
CRT	central retinal thickness
CRVO	central retinal vein occlusion
CSR	clinical study report
CTFG	Clinical Trials Facilitation group
DME	diabetic macular edema
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ePRO	electronic patient-reported outcome
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EudraCT	EU Drug Regulating Authorities Clinical Trials
FA	fluorescein angiography
FAS	full analysis set
FP	fundus photography
GCL	global clinical leader
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HR	heart rate
HDL	high-density lipoprotein
IA	Interviewer-administered format
IAI	intravitreal aflibercept injection
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IOP	intraocular pressure
IRB	institutional review board
IV	intravenous
IVRS	interactive voice response system
IVT	intravitreal(ly)
IWRS	interactive web response system
IxRS	Interactive voice/web response system
LOCF	last observation carried forward
LSmean	least squares mean
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
mCNV	myopic choroidal neovascularization
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NaCl	Sodium chloride
nAMD	neovascular AMD
NEI VFQ-25	National Eye Institute 25-item Visual Function Questionnaire
OCT	optical coherence tomography
PlGF	placental growth factor
PID	patient identification number
PPS	per-protocol set
PT	prothrombin time
PTT	partial thromboplastin time
RAVE	Electronic data capture system
SAE	serious adverse event
SAP	statistical Analysis Plan
SAS	Statistical analysis system
SC	subcutaneous
SF-36	Short form health survey 36-item
SmPC	Summary of product characteristics
SMT	safety management team
SOC	system organ class
StM	study manager
SUSAR	suspected, unexpected, serious adverse reaction
TOSCA	Tools for syntactic corpus analysis
UPCR	urine protein/creatinine ratio
US	United States
VA	visual acuity
VEGF	vascular endothelial growth factor
WHO DD	World Health Organisation Drug Dictionary
YAG	yttrium aluminum garnet

3. Introduction

3.1 Background - amended

Age-related macular degeneration (AMD) is a leading cause of adult blindness in the developed world (Rahmani et al. 1996). 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 (Aiello et al. 1994). Anti-VEGF therapy has been shown to provide significant therapeutic benefit to patients suffering from nAMD.

To date, aflibercept has been approved as a treatment for nAMD, macular edema secondary to central retinal vein occlusion (CRVO), diabetic macular edema (DME), and macular edema secondary to branch retinal vein occlusion (BRVO) in the United States (US), European Union (EU), Japan, and other countries; as well as for myopic choroidal neovascularization (mCNV) in the EU, Japan and other countries; and for diabetic retinopathy in patients with DME in the US.[12]

The approval of aflibercept in the EU (27 November 2012) was based upon the results of two randomized, multicenter, double-masked, active-controlled Phase-3 clinical studies — the VIEW 1 (US and Canada) and VIEW 2 (EU, Asia/Pacific, and Latin America) studies. Both studies demonstrated that aflibercept, dosed every 8 weeks following three initial monthly injections, provided efficacy that was clinically equivalent to the former standard of care, Lucentis (ranibizumab injection) dosed monthly. The primary endpoint of these studies was the maintenance of visual acuity (less than 15 letters of vision lost on the Early Treatment Diabetic Retinopathy Study [ETDRS] chart) over 52 weeks. During the second year of these studies, the treatment interval could be extended (based on protocol-specified re-treatment criteria), with no more than 12 weeks allowed between injections. Because the extended treatment interval was capped at 12 weeks, the present study is being conducted to assess the option to extend the treatment interval with no additional restrictions (i.e. no maximum limit to the treatment interval).

The approved EU labeling for aflibercept states:

> The recommended dose for Eylea is 2 mg aflibercept, equivalent to 50 microliters.
>
> Eylea treatment is initiated with one injection per month for three consecutive doses, followed by one injection every two 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.

12 Update of approved indications for aflibercept by country per Amendment 2 (Section 15.1.1.1)

3.2 Rationale of the study

As a condition for approval, the European Medicines Agency (EMA) has required a study to assess every-other-month dosing versus an extended-dosing regimen with no maximum limit to the treatment interval. This Phase-3b post-authorization efficacy study has been designed to meet this obligation and compares a fixed dosing regimen of 2 mg aflibercept administered every 8 weeks ("2Q8 group") to a flexible extended regimen of 2 mg aflibercept ("extended-dosing group") in patients with nAMD who have completed at least 1 year of treatment with aflibercept.

3.3 Benefit-risk assessment

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

The risks of the local IVT application are limited to ocular adverse events (AEs). There is no indication that local application causes systemic AEs. Proteinuria and hypertension are potential systemic effects from intravenous (IV) or subcutaneous (SC) 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, would not be expected to have clinically significant systemic effects. The risks associated with IVT administration of VEGF Trap-Eye observed in the Phase-3 studies are thought to be similar to those of IVT administration of pegaptanib sodium and ranibizumab.

Taken together, the data indicate that the new therapy (VEGF Trap Eye) has a favorable benefit-risk ratio. In particular, subjects enrolled into this study are not seen as being exposed to an undue risk.

4. Study objectives

Primary objective

To compare the efficacy of 2 mg aflibercept administered by two different intravitreal (IVT) treatment regimens to subjects with nAMD.

Secondary objective

To assess the safety and tolerability of aflibercept in this patient population

5. Study design - amended

Design overview

This is a randomized, 2-arm, active-controlled, parallel-group, open-label, multicenter, Phase-3b study to assess the non-inferiority of an extended-dosing regimen to a 2Q8 fixed dosing regimen in subjects with nAMD who have completed at least 1 year of treatment with aflibercept (from first treatment to randomization into this study) in accordance with the constraints as provided in this protocol.

This study comprises a screening period of up to 66 days (Figure 5–1).[13]

There will be two parallel treatment arms. In both arms, aflibercept will be injected IVT at a dose of 2 mg per injection. The treatment arms differ in dosing intervals:

Extended dosing: Flexible dosing intervals

≥8 weeks (no upper limit) based on visual and anatomic outcomes as judged by the investigator.

When/if visual and 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 were observed).

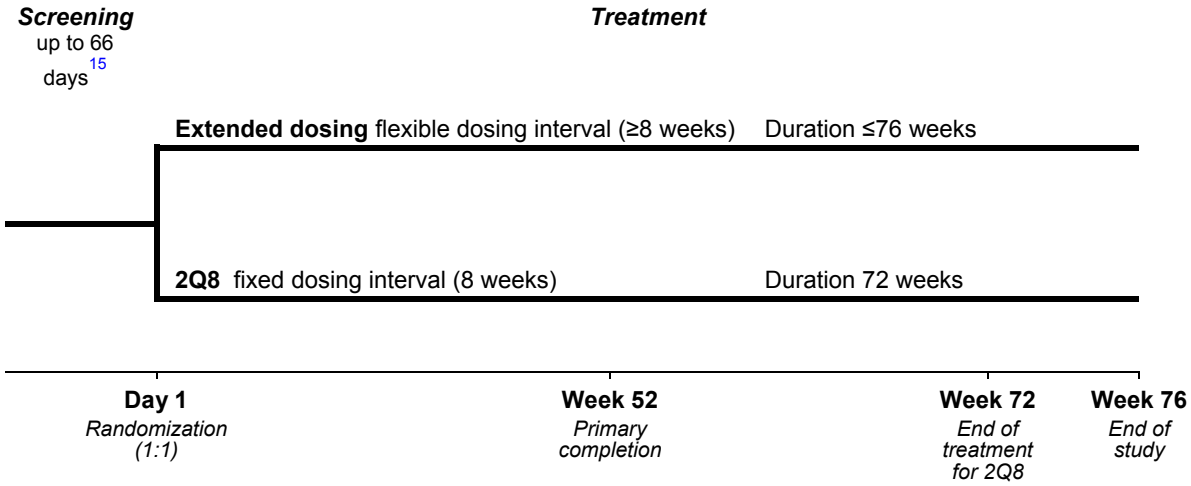
2Q8: Fixed dosing intervals

8 weeks - modification of the treatment interval is not allowed.[14]

13 Clarification of the period durations per Amendment 2 (Section 15.1.1.2)

14 Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline per Amendment 2 (Section 15.1.1.3)

Figure 5–1: Study flow diagram - amended



Following screening, eligible subjects will be randomized (1:1) to one of the two parallel treatment group. Two post-baseline visits will follow the same strict schedule in both treatment groups: primary completion at Week 52 and the final visit at Week 76. The schedule of all other post-baseline visits may differ between the treatment groups as detailed in Section 9.[15]

Subjects in both treatment groups will receive the first study treatment on Day 1. The treatment period is 72 weeks (in the 2Q8 group) with a final study visit at Week 76.[15]

The last possible study drug injection in the extended-dosing group can be given at Week 76 (i.e. the end of the study) after completion of all protocol-specified assessments.[16] After Week 76, subjects should be returned to standard of care.

For each treatment group, the time window for all post-baseline visits is ± 3 days relative to baseline.[17]

The **primary efficacy variable** will be the change in ETDRS BCVA letter score for the study eye (starting at 4 meters) from baseline to Week 52. A complete list of all efficacy variables is provided in Section 10.3.1.1. Both the primary and secondary efficacy variables will be assessed at Week 52/last observation carried forward (LOCF). The primary analysis will be based on the Full Analysis Set.

15 Clarification of the period durations per Amendment 2 (Section 15.1.1.2)

16 If an extended-dosing subject receives an injection at Week 76, it is the responsibility of the treating investigator to follow-up on any adverse events (including ongoing events) that may occur within 4 weeks following this treatment. Information regarding such events is to be reported under this protocol (i.e. not as spontaneous reports).

17 Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline per Amendment 2 (Section 15.1.1.3).

Assessments of **ocular safety** will include intraocular pressure (IOP), indirect ophthalmoscopy, and slit lamp biomicroscopy. Under this protocol, mandatory fluorescein angiography (FA)/fundus photography (FP) examinations will be conducted during screening as well as at Week 52 and 76 only. However, the treating investigator may perform FA/FP at other times during the study based on his/her medical judgment and standard of care.

Overall safety of the subjects will be assessed throughout the study by recording vital signs as well as by monitoring ophthalmic and systemic adverse events (AEs). Laboratory tests (hematology panel, chemistry panel, and urinalysis) will be performed at baseline and Week 76.

Justification of the design

Open-label setting: Since the two treatment groups will be on different visit schedules (i.e. a fixed schedule in the 2Q8 group and a variable schedule in the extended-dosing group), masking the study would be extremely difficult. Masking the study would require harmonizing the schedules in the two groups by having subjects in the extended-dosing group attend non-treatment study visits. Doing this, however, would disrupt the intent of an extended-dosing regimen and, thus, was not considered to be a viable option.

End of study

For each participating EU country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last subject for all centers in the respective country has occurred.

The end of the study as a whole will be reached as soon as the end of the study according to the above definition has been reached in all participating countries (EU and non-EU).

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.

Two sets of inclusion/exclusion criteria, as described below, will be used to select subjects for participation in this study. All inclusion/exclusion criteria will be assessed during the screening phase and the subject must sign the informed consent form before any of the inclusion/exclusion criteria are assessed. In order to be randomized into this study, a subject must meet ALL of the eligibility criteria in both sets of criteria.

Two sets of inclusion and exclusion criteria will be used to select subjects for participation in this study:

- The **first set** of inclusion/exclusion criteria will be based on the subject's medical history prior to initiation of treatment with marketed aflibercept and will be assessed by a review of the subject's medical records. This will ensure that the subject's pre-aflibercept status matches, as close as possible, the baseline criteria of the pivotal VIEW program.
- The **second set** of inclusion/exclusion criteria considers both the subject's medical history (assessed by a review of the subject's medical records) and the actual status of the subject at the time of signing the informed consent form (i.e. at enrollment into the study via conduct of study-specific screening procedures).

All inclusion/exclusion criteria will be assessed during the screening phase, and the subject must sign the informed consent form before any of the inclusion/exclusion criteria are assessed. Fluorescein angiography and fundus photography eligibility criteria will be checked against (i) images taken at the time of nAMD diagnosis and initiation of treatment with aflibercept and (ii) images obtained during the study screening period. In order to be randomized into this study, a subject must meet ALL of the eligibility criteria in both sets of criteria.

Only one eye will be designated as the study eye. For subjects who meet eligibility criteria in both eyes during the screening phase, the eye with the worse visual acuity (VA) will be selected as the study eye.[18] If both eyes have equal VA, 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.

18 Clarification of the procedure of selecting the study eye per Amendment 2 (Section 15.1.1.4)

6.1 Inclusion criteria

6.1.1 First set of inclusion criteria - amended

All of the following criteria must have been met at the initial start of aflibercept treatment (i.e. start of aflibercept treatment prior to this study) for a subject to be eligible for this study.

1. Subject had primary subfoveal choroidal neovascularization (CNV) lesions secondary to nAMD, including juxtafoveal lesions that affect the fovea, as evidenced by FA of the study eye within 4 weeks before the initiation of aflibercept treatment.[19,20,21]
2. The area of CNV occupied at least 50% of the total lesion within 4 weeks before the initiation of aflibercept treatment.[21]
3. Documented BCVA was 20/40 to 20/320 (comparable to a letter score of 73 to 25) in the study eye at the initiation of treatment (the initial BCVA of the study eye before treatment initiation must be documented as Snellen equivalent in the electronic case report form [eCRF]).[22, 23]

6.1.2 Second set of inclusion criteria - amended

All of the following criteria must be met at the time of screening for participation in this study for a subject to be eligible for this study.

4. Signed written informed consent[22]
5. Men or women ≥ 51 years of age
6. The subject's history of aflibercept treatment meets ALL of the following:
   a) Treatment in the study eye was initiated with three monthly (-1 week/+2 weeks) doses of 2 mg aflibercept and improvements of visual and anatomic outcomes were observed
   b) Following the above initiation phase, the intervals between treatments were between 6 weeks and 12 weeks (one exception will be allowed)
   c) The interval between the last two pre-study injections was ≥8 weeks, and visual and anatomic outcomes have been stable over this interval.
   d) The subject received the last IVT injection of aflibercept in the study eye 2 months (±10 days) before the first treatment in this study[22]

19 The reading center acquisition protocol will further specify the standards for FA during the study (replaced reference of study manual with reference to reading center acquisition protocol per Amendment 2 [Section 15.1.1.7])

20 Clarifications of inclusion criteria per Amendment 2 (Section 15.1.1.5)

21 Extension of the time period per Amendment 2 (Section 15.1.1.6)

22 Clarifications of inclusion criteria per Amendment 2 (Section 15.1.1.5)

23 Removal of reference to study manual per Amendment 2 (Section 15.1.1.7)

e) Total prior treatment duration with aflibercept (i.e. from first treatment to randomization into this study) was ≥12 months

7. Subject is willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
8. Women and men of reproductive potential must agree to a method of highly effective contraception (as defined by the Clinical Trial Facilitation Group [CTFG] from 15 SEP 2014):[24]

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

Alternatively women and men of reproductive potential can also use two acceptable methods of contraception (as defined by the CTFG from 15 SEP 2014) simultaneously:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide

Contraception has to be used from signing the informed consent form until 3 months after the last administration of study drug. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of child bearing potential.

24 Use of contraception specified according to the recommendations of the CTFG per Amendment 2 (Section 15.1.1.8).

6.2 Exclusion criteria

6.2.1 First set of exclusion criteria

A subject who has met any of the following criteria at the initial start of aflibercept treatment (i.e. start of aflibercept treatment before this study) will be excluded from this study.

1. Any prior or concomitant therapy with an investigational or approved agent to treat neovascular AMD in the study eye.
2. Total lesion size >12 disc areas (30.5 mm^2, including blood, scars and neovascularization) as assessed by FA in the study eye
3. Subretinal hemorrhage that was:
   a) 50% or more of the total lesion area, or
   b) if the blood was under the fovea, and
   c) the blood under the fovea was 1 or more disc areas in size in the study eye.
4. Scar or fibrosis making up more than 50% of the total lesion in the study eye.
5. Scar, fibrosis, or atrophy involving the center of the fovea in the study eye.
6. Presence of retinal pigment epithelial tears or rips involving the macula in the study eye.
7. Causes of CNV other than AMD in the study eye.

6.2.2 Second set of exclusion criteria - amended

A subject who meets any of the following criteria at the time of screening for participation in this study will be excluded from this study.

8. Subjects who currently meet any of the first set of exclusion criteria with the exception of prior treatment with aflibercept
9. Any prior ocular (in the study eye) or systemic treatment or surgery for neovascular AMD, except dietary supplements, vitamins and IVT injections of aflibercept, during the time (i.e. at least 12 months) between initiation of aflibercept treatment and randomization into this study
10. Any prior treatment with anti-VEGF therapy in the study eye, with the exception of IVT injections of aflibercept, during the time (i.e. at least 12 months) between initiation of aflibercept treatment and randomization into this study
11. Prior systemic anti-VEGF therapy, investigational or approved, within the last 15 months prior to randomization
12. Any vitreous hemorrhage within 4 weeks before randomization in the study eye[25]
13. Active intraocular, extraocular and periocular inflammation or infection in either eye

25 Clarifications added per Amendment 2 (Section 15.1.1.9)

14. Any ocular or periocular infection within 4 weeks of randomization in either eye[25]
15. Any serious adverse event related to aflibercept during prior treatment (see Sections 9.6.1.1 and 9.6.1.2)
16. Any history of allergy or hypersensitivity to povidone iodine[25]
17. Known serious allergy or hypersensitivity to the fluorescein sodium for injection in angiography[25]
18. Presence of any contraindications indicated in the EU commission/locally approved label for aflibercept: Hypersensitivity to the active substance aflibercept or to any of the excipients; active or suspected ocular or periocular infection; active severe intraocular inflammation
19. Prior vitrectomy in the study eye
20. History of vitreomacular traction in the study eye [25]
21. History of retinal detachment or treatment or surgery for retinal detachment in the study eye
22. Any history of macular hole of stage 2 and above in the study eye
23. Prior trabeculectomy or other filtration surgery in the study eye
24. Uncontrolled glaucoma (defined as intraocular pressure more than 25 mmHg despite treatment with antiglaucoma medication) in the study eye
25. Aphakia or pseudophakia with absence of posterior capsule (unless it occurred as a result of an yttrium aluminum garnet [YAG] posterior capsulotomy) in the study eye
26. Previous therapeutic radiation in the region of the study eye
27. History of corneal transplant or corneal dystrophy in the study eye
28. Significant media opacities, including cataract, in the study eye that interferes with visual acuity or fundus photography
29. History or clinical evidence of DME or any retinal vascular disease other than AMD in either eye
30. Any history of uveitis in either eye
31. Presence of scleromalacia in either eye
32. Pregnancy or breast-feeding (women only)
33. The use of long acting steroids, either systemically or intraocular, in the 18 months before initiating study treatment (or Iluvien IVT implant at any time)[26]
34. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that

26 Clarifications added per Amendment 2 (Section 15.1.1.9)

contraindicates the use of an investigational drug, might affect interpretation of the results of the study, or renders the subject at high risk for treatment complications

35. Previous assignment to treatment during this study
36. Concomitant participation in another clinical study with investigational medicinal product(s)
37. 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).

6.3 Withdrawal of subjects from 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 two consecutive pre-planned study visits without a major reason agreed upon by the sponsor. All attempts to contact the subject must be documented in the subject's source documents.
- Relevant laboratory abnormality or 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 AMD 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.

- Decision by the investigator or sponsor 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).

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

Screening failure

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

Re-screening of screening failures may be acceptable under the following conditions[27]:

- The subject had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- The inclusion / exclusion criteria preventing the subject's initial attempt to participate have been changed (see inclusion criterion 1 and 2 changed via this protocol amendment).
- The reason for the screening failure was subsequently resolved (e.g. elevated IOP decreases, inflammation or infection resolves) 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 has to sign a new informed consent form. To be eligible, re-screened subjects must meet all eligibility criteria during the re-screening period.

Dropout

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

27 Added list of criteria for re-screening per Amendment 2 (Section 15.1.1.10)

General procedures

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

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

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

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

6.3.2 Replacement

Subjects who withdraw from the study will not be replaced.

6.4 Subject identification - amended

The subject number is a 9 digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current subject number within the center

Patient identification numbers (PIDs) will be assigned via interactive voice/web response system (IxRS). Once allocated, the subject's PID number will identify the subject throughout the study, and will be entered into the Site Enrollment Log and on the eCRF.

Upon re-screening, a new PID will be assigned.[28]

28 Description of subject identification number changed per Amendment 2 (Section 15.1.1.11)

7. Treatments

7.1 Treatments to be administered - amended

There will be two parallel treatment arms, each administering 2 mg aflibercept per injection IVT in the study eye. Aflibercept will be administered either on a fixed 2Q8 schedule (i.e. 2 mg aflibercept every 8 weeks[29]) or according to an extended-dosing protocol in which the dosing interval may be extended beyond 8 weeks based on visual and anatomical outcomes and knowledge of the individual subject as judged by the treating investigator (Table 7–1).

Table 7–1: Treatment groups - amended

	Extended-dosing group	2Q8 group
Dose per injection	Aflibercept 2 mg	Aflibercept 2 mg
Administration schedule[a]	Flexible injection intervals: ≥8 weeks When/if exudation recurs, the treatment interval will revert to the last treatment interval in which the disease was inactive. Interval decisions based investigator's judgment. Intervals cannot be less than 8 weeks (no upper limit).	Fixed injection intervals: 8 weeks throughout the entire treatment period[29]
Duration of treatment	up to 76 weeks	72 weeks
Planned number of randomized subjects	165	165

[a] For each treatment group, the time window for all post-baseline visits is ± 3 days relative to baseline[29]

29 Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline per Amendment 2 (Section 15.1.1.3)

7.2 Identity of study treatment - amended

The identity of the study drug is summarized in Table 7–2.[30]

Table 7–2: Identity of study drug

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

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

For all study drugs, a system of numbering in accordance with all requirements of 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.

7.3 Treatment assignment

Subjects enrolled in the study will be randomized to receive treatment under one of two dosing regimens. The two treatment groups will be randomly assigned by the central randomization group in a 1:1 ratio to either of the two parallel treatment arms identified in Section 7.1. Treatment assignment will be controlled via the IVRS/IWRS.

30 Table added specifying the identity of study drug per Amendment 2 (Section 15.1.1.12)

7.4 Dosage and administration - amended

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

- Sterile study drug in sealed glass vials (2 mL) with a withdrawable volume of 0.1 mL (see Table 7–2 for details on the composition of the study drug)
- Filter needle (18 gauge)

Other ancillary components required for the administration of aflibercept (e.g. 30-gauge injection needle; 1-ml syringe) will be supplied by the study site.

When aflibercept vials are removed from the refrigerator, the solution should be visually inspected and it should have no evidence of turbidity. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

After opening the vial, all preparation steps have to take place under aseptic conditions.

The study drug will be withdrawn using aseptic technique through the filter needle attached to the 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 by the sterile 30-gauge needle for the IVT injection. Each patient receives an IVT injection of 50 µl of aflibercept. [31]

Consideration of special warnings from EU label

The investigator should consider the special warnings as described in the EU label for aflibercept. However, ultimately the investigator should include in his/her treatment decision all subject related information and data available and based on this decide what would be best for the subject.

The approved EU label for aflibercept includes the following special warnings:

> Treatment should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes. In the event of a retinal break, the dose should be withheld and treatment should not be resumed until the break is adequately repaired.
>
> The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of:
>
> - a decrease in BCVA of ≥30 letters compared with the last assessment of visual acuity;
> - a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50%, of the total lesion area
>
> The dose should be withheld within the previous or next 28 days in the event of a performed or planned intraocular surgery.[32]

31 Removed sample study drug injection protocol from the appendix per Amendment 2 (Section 15.1.1.20).

32 Dosage and administration updated and special warnings from EU SmPC added to dosage and administration per Amendment 2 (Section 15.1.1.13)

Posology

Treatment posology is detailed in Table 7–3.[33]

Table 7–3: Treatment posology

	2Q8 group		Extended-dosing group	
	Visit	Treatment	Visit	Treatment
Baseline	mandatory Visit 2	mandatory	mandatory Visit 2	mandatory
Week 8	mandatory visit with treatment		*between Week 8 and Week 52, visits (including treatment) can be scheduled at any timepoint (provided injection intervals are ≥8 weeks)*	
Week 16	mandatory visit with treatment			
Week 24	mandatory visit with treatment			
Week 32	mandatory visit with treatment			
Week 40	mandatory visit with treatment			
Week 48	mandatory visit with treatment			
Week 52	**mandatory**	**no treatment**	**mandatory**	**optional**
Week 56	mandatory visit with treatment		*between Week 52 and Week 76, visits (including treatment) can be scheduled at any timepoint (provided injection intervals are ≥8 weeks)*	
Week 64	mandatory visit with treatment			
Week 72	mandatory visit with treatment			
Week 76	**mandatory**	**no treatment**	**mandatory**	**optional**

7.5 Blinding / masking

Not applicable - this is an open-label study.

7.6 Drug logistics and accountability - amended

Packaging

Aflibercept will be supplied by the Sponsor in a 2-mL glass vial. The extractable volume is 0.1 mL. Each kit will also contain an 18-gauge filter needle. Other ancillary components required for the administration of aflibercept (e.g. 30-g x ½ inch injection needle and 1-mL Luer Lock syringe) will be supplied by the study site.

33 Added table describing treatment posology per Amendment 2 (Section 15.1.1.14)

Storage

All study drugs will be stored at the investigational site in accordance with GCP and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/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's study file; the site-relevant elements of this information will be available in the investigator site file.

Aflibercept must be stored at the clinical sites in a refrigerator at 2°C to 8°C, protected from light, and not frozen. Prior to usage, the unopened vial of aflibercept may be stored at room temperature (25 °C / 77°F) for up to 24 hours. After opening the vial or blister pack, proceed under aseptic conditions.[34]

Accountability

On the day of receipt, the responsible site personnel will confirm receipt of study drug via IVRS/IWRS. 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.

If performing drug accountability implies a potential risk of contamination, a safety process/ guidance for handling returned drug will be provided.

7.7 Treatment compliance

As all study drugs will be administered in a medical facility by authorized site personnel, compliance with the dosing protocol will be monitored by review of clinic records.

34 Paragraph added per Amendment 2 (Section 15.1.1.15).

8. Non-study therapy

Any relevant previous and concomitant treatments will be recorded in the source documentation and then entered into the "Previous and Concomitant Medications" eCRF screen using the brand name.

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

8.1 Prior and concomitant therapy

8.1.1 Prior therapy

In particular, any potential previous treatments for AMD will be recorded, including treatment with anti VEGF medication, steroids or laser.

Prior treatments that exclude subjects from participation in this study are given in Section 6.2.

8.1.2 Concomitant therapy

Any medication 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 below.

8.1.2.1 Study-eye treatment - amended

Subjects may not receive any standard or investigational agents for treatment of their AMD in the study eye other than aflibercept as specified in this protocol until they have completed the final or early termination visit assessments.[35] This includes medications administered locally (e.g. IVT, by juxtascleral or periorbital routes), as well as those administered systemically with the intent of treating the fellow eye.

8.1.2.2 Fellow-eye treatment - amended

Treatment of the fellow (non-study) eye is not regarded as a study treatment. If the fellow eye has AMD, the fellow eye may receive any locally approved non-systemic treatment. If the fellow eye shall be treated pharmacologically, the most appropriate treatment option that is approved by the governing health authorities may be selected at the investigator's discretion in the subject's best interest.

35 Clarified that the final visit procedures should also be conducted in the case of early termination per Amendment 2 (Section 15.1.1.16)

If no drug therapy has been approved for the indication or if the approved therapy is not appropriate due to medical reasons, a non-approved pharmacological approach may be selected, if it can be considered as local standard of care.[36]

If it is determined that aflibercept is the most appropriate treatment option for the fellow eye, this will still not be regarded as a study treatment and 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.

8.2 Post-study therapy

After the end of this study, subjects will not be restricted with regard to pursuing available treatments for AMD.

9. Procedures and variables - amended

The study comprises a screening phase (Visit 1; up to 66 days prior to Day 1), Baseline (Visit 2, Day 1), a 72-week treatment phase (for the 2Q8 group), and a final study visit at Week 76 or an early termination visit.[37] All scheduled post-baseline study visits may deviate by ± 3 days relative to baseline.[38]

36 Added possibility to treat the fellow eye with any local standard of care per Amendment 2 (Section 15.1.1.34)

37 Clarified that the final visit procedures should also be conducted in the case of early termination per Amendment 2 (Section 15.1.1.16)

38 Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline per Amendment 2 (Section 15.1.1.3) and clarification of the period durations per Amendment 2 (Section 15.1.1.2)

9.1 Tabular schedule of evaluations - amended

Table 9–1: Schedule of assessments and study procedures - amended

Visit number [a]	*Screening* **Visit 1**	*Baseline (BL)* **Visit 2**	**Visits 3 - 8**	*Prim. compl.* **Visit 9**	**Visits 10 - 12**	*Final visit* **Visit 13**[39] *or early term.*
Time point[a] **2Q8 group** / **Extended-dosing group**	**up to 66 days prior to BL**[40] (both groups)	**Day 1** (both groups)	**Weeks 8 – 48** / **Flex. intervals** (≥8 weeks)	**Week 52** (both groups)	**Week 56, 64, 72** / Flex. intervals (≥8 weeks)	**Week 76** (both groups)
Initiation procedures						
Informed consent	●					
Demographic data	●					
Medical / ophthalmic history	●					
Physical examination	●					
PT / INR and PTT	●					
Inclusion / exclusion criteria	●	●				
Study medication						
Randomization		●				
Administration of study treatment [41]		●	●	extended-dosing only [b]	●	extended-dosing only [b,c]
Ophthalmologic assessments						
BCVA (ETDRS chart starting at 4 m) [d]	●	●	●	●	●	●
Optical coherence tomography	●	●	●	●	●	●
FA, FP	●			●		●
Indirect ophthalmoscopy [e]	●	●	●	●	●	●
Slit lamp biomicroscopy	●	●	●	●	●	●
Intraocular pressure (IOP) [f]	●	●	●	●	●	●

a: All post-baseline visits may deviate by ± 3 days relative to baseline. In the 2Q8 group, scheduled visits should not be altered due to the deviation of the previous visit.[42]
Visit numbers refer to the mandatory visits for treatment administration to subjects in the 2Q8 group. Fewer visits may be required for subjects in the extended-dosing group, for whom extended-dosing intervals are indicated.

b: Extended-dosing subjects may receive injections at Week 52 or 76 depending on their individual schedule.

c: If an extended-dosing subject receives an injection at Week 76, follow-up is needed on any adverse events (including ongoing events) that may occur within 4 weeks following this treatment (AE reporting under this protocol; i.e. not as spontaneous reports)

d: Refraction to be done at each visit

e: Also post-injection at visits with study drug administration[43]

f: Also 30-60 minutes post-injection at visits with study drug administration[43]

(Table continued on next page)

39 Clarified that the final visit procedures should also be conducted in the case of early termination per Amendment 2 (Section 15.1.1.16)

40 Clarification of the period duration per Amendment 2 (Section 15.1.1.2)

41 Removed sample study drug injection protocol from the appendix per Amendment 2 (Section 15.1.1.20)

42 Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline and clarification of the schedule of visits in the 2Q8 group per Amendment 2 (Section 15.1.1.3)

43 Minor clarifications per Amendment 2 (Section 15.1.1.19)

Table 9–1 (continued) Schedule of assessments and study procedures - amended

Visit number [a]	*Screening* Visit 1	*Baseline (BL)* Visit 2	Visits 3 - 8	*Prim. compl.* Visit 9	Visits 10 - 12	*Final visit* Visit 13[44] *or early term.*
Time point[a] 2Q8 group / Extended-dosing group	up to 66 days prior to BL[45] (both groups)	Day 1 (both groups)	Weeks 8 – 48 / Flex. intervals (≥8 weeks)	Week 52 (both groups)	Week 56, 64, 72 / Flex. intervals (≥8 weeks)	Week 76 (both groups)
Standard safety						
Prior / concomitant medications	●	●	●	●	●	●
Adverse events [g]		●	●	●	●	●
Vital signs (temp., blood pressure, HR)	●	●	●	●	●	●
Hematology / chemistry	●					●
Urinalysis / UPCR	●					●
Serum pregnancy test (women of childbearing potential only) [46]	●					
Urine dipstick pregnancy test (women of childbearing potential only) [47] [h]		●				●
Other						
NEI VFQ-25 [i]		●		●		●

BCVA = Best corrected visual acuity; early term. = early termination; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography FP = fundus photography; HR = heart rate; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; PT/INR = Prothrombin time / International normalized ratio; PTT = Partial thromboplastin time; UPCR = Urine protein/creatinine ratio

a: All post-baseline visits may deviate by ± 3 days relative to baseline. In the 2Q8 group, scheduled visits should not be altered due to the deviation of the previous visit.[48]

Visit numbers refer to the mandatory visits for treatment administration to subjects in the 2Q8 group. Fewer visits may be required for subjects in the extended-dosing group, for whom extended-dosing intervals are indicated.

g: Any AE occurring up to 4 weeks after the last injection of aflibercept has to be documented, regardless of the relationship to the study drug or the seriousness of the event and reported in accordance with this protocol (i.e. not as a spontaneous report). For any drug-related AE occurring after 4 weeks after the last application of aflibercept, the standard procedures that are in place for spontaneous reporting will be followed.

h: The urine dipstick pregnancy test is to be repeated as frequently as required following the investigator's medical judgment and local regulations.[47]

i: The NEI VFQ-25 is to be administered in a quiet room by a person certified to administer the questionnaire[49]

44 Clarified that the final visit procedures should also be conducted in the case of early termination per Amendment 2 (Section 15.1.1.16)

45 Clarification of the period duration per Amendment 2 (Section 15.1.1.2)

46 Moved the serum pregnancy test from Initiation procedures to Standard safety per Amendment 2 (Section 15.1.1.18)

47 Addition of urine dipstick test at the baseline visit per Amendment 2 (Section 15.1.1.17); added foot note h and added that the urine dipstick test is required at Visit 13 (final visit or early termination) per Amendment 2 (Section 15.1.1.18)

48 Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline and clarification of the schedule of visits in the 2Q8 group per Amendment 2 (Section 15.1.1.3)

49 Footnotes re-arranged and separated table to 2 pages per Amendment 2 (Section 15.1.1.19)

9.2 Visit description

9.2.1 Screening visit (Visit 1) - amended

Scheduling: Both treatment groups: Up to 66 days prior to Day 1[50]

The following procedures will be performed at this visit:

- Obtaining signed informed consent form (see Section 13.4 for details).
- Assessment of inclusion and exclusion criteria (see Sections 6.1 and 6.2 for details)
- Record of demographic data (see Section 9.3.1 for details)
- Record of medical and ophthalmic history (see Section 9.3.2 for details)
- Laboratory assessments (see Section 9.6.3.1 for details):
  - Hematology panel
  - Chemistry panel, including serum pregnancy test for women of childbearing potential
  - Prothrombin time/partial thromboplastin time (PT/PTT) and INR
  - Urinalysis (including urine protein creatinine ratio [UPCR]) – Note: urine sample must be obtained before performing FA in order to avoid false elevations in urine protein values
- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Fundus photography (FP) and fluorescein angiography (FA)[51]
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intra-ocular pressure (IOP)
- Record of prior and concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Physical examination (see Section 9.6.3.2 for details)
- Vital signs (body temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)

50 Clarification of the period duration per Amendment 2 (Section 15.1.1.2)

51 The reading center acquisition protocol will further specify the standards for FA/FP during the study (replaced reference of study manual with reference to reading center acquisition protocol per Amendment 2 [Section 15.1.1.7]).

9.2.2 Baseline visit (Visit 2) - amended

Scheduling: Both treatment groups: Day 1

The following procedures will be performed at this visit:

- Re-check of inclusion and exclusion criteria (see Sections 6.1 and 6.2 for details)[52]
  - Including urine dip stick pregnancy test for women of childbearing potential[53]
- Randomization (see Section 7.3 for details)
- Record of concomitant medications (see Section 8.1 for details)
- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intra-ocular pressure (IOP)
- Record of NEI VFQ-25 (see Section 9.7 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Vital signs (body temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Application of study medication (see Section 7.4 for details)
- Post-injection ocular assessments (see Section 9.4.1 for details):[54]
  - Indirect ophthalmoscopy
  - Intraocular pressure (IOP)

52 Clarified the re-assessment of inclusion and exclusion criteria per Amendment 2 (Section 15.1.1.21)

53 Addition of urine dipstick test at the baseline visit per Amendment 2 (Section 15.1.1.17)

54 Post-injection ocular assessments added per Amendment 2 (Section 15.1.1.22)

9.2.3 Visits between baseline and Week 52 - amended

The scheduling of these visits may vary between both treatment groups:

Scheduling:

- 2Q8 group: Fixed visit schedule every 8 weeks
  Visits 3 to 8
- Extended-dosing group: Individualized flexible schedule with intervals ≥8 weeks
  Visits 3 to ≤8 (extended-dosing subjects may have fewer visits than 2Q8 subjects)

The following procedures will be performed at any of these visits:

- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intra-ocular pressure (IOP)
- Record of concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Vital signs (body temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Application of study medication (see Section 7.4 for details)
- Post-injection ocular assessments (see Section 9.4.1 for details):[55]
  - Indirect ophthalmoscopy
  - Intraocular pressure (IOP)

55 Post-injection ocular assessments added per Amendment 2 (Section 15.1.1.22)

9.2.4 Primary completion (Week 52) - amended

Scheduling: Both treatment groups: Week 52

- 2Q8 group: **Visit 9**
- Extended dosing group: **Visit ≤9**
  Visit number depends on individual schedule (extended-dosing subjects may have fewer visits than 2Q8 subjects)

The following procedures will be performed at this visit:

- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Fundus photography (FP) and fluorescein angiography (FA)[56]
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intra-ocular pressure (IOP)
- Record of concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Vital signs (body temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Record of NEI VFQ-25 (see Section 9.7 for details)

Subjects in the extended dosing group if they receive injections at this visit (depending on their individual schedule):

- Application of study medication (see Section 7.4 for details)
- Post-injection ocular assessments (see Section 9.4.1 for details):[57]
  - Indirect ophthalmoscopy
  - Intraocular pressure (IOP)

56 The reading center acquisition protocol will further specify the standards for FA/FP during the study (replaced reference of study manual with reference to reading center acquisition protocol per Amendment 2 [Section 15.1.1.7]).

57 Post-injection ocular assessments for subjects in the extended dosing group who receive study medication at this visit added per Amendment 2 (Section 15.1.1.22)

9.2.5 Visits between primary completion (Week 52) and final visit (Week 76) - amended

Scheduling[58]:

– 2Q8 group:	Fixed visit schedule every 8 weeks **Visits 10 (Week 56) to 12 (Week 72)**
– Extended-dosing group:	Individualized flexible schedule with intervals ≥8 weeks **Visit numbers depend on individual schedule** (extended-dosing subjects may have fewer visits than 2Q8 subjects)

The following procedures will be performed at any of these visits:[59]

- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intra-ocular pressure (IOP)
- Record of concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Vital signs (body temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Application of study medication (see Section 7.4 for details)
- Post-injection ocular assessments (see Section 9.4.1 for details):[60]
  - Indirect ophthalmoscopy
  - Intraocular pressure (IOP)

58 Changed end of study visit to final visit per Amendment 2 (Section 15.1.1.16)

59 Added the full list of study procedures instead of a reference only per Amendment 2 (Section 15.1.1.23)

60 Post-injection ocular assessments added per Amendment 2 (Section 15.1.1.22)

9.2.6 Final visit (Week 76) or early termination- amended

Scheduling: Both treatment groups: Week 76

This visit will also be conducted in case of early termination of a subject.[61]

The following procedures will be performed at this visit:[62]

- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Fundus photography (FP) and fluorescein angiography (FA)[63]
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intra-ocular pressure (IOP)
- Record of concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Vital signs (body temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Urine dip stick pregnancy test for women of childbearing potential[64]
- Record of NEI VFQ-25 (see Section 9.7 for details)

Subjects in the extended dosing group if they receive injections at this visit (depending on their individual schedule):

- Application of study medication (see Section 7.4 for details)
- Post-injection ocular assessments (see Section 9.4.1 for details):[65]
  - Indirect ophthalmoscopy
  - Intraocular pressure (IOP)

61 Clarified that the final visit procedures should also be conducted in the case of early termination per Amendment 2 (Section 15.1.1.16)

62 Added the full list of study procedures instead of a reference only per Amendment 2 (Section 15.1.1.23)

63 The reading center acquisition protocol will further specify the standards for FA/FP during the study (replaced reference of study manual with reference to reading center acquisition protocol per Amendment 2 [Section 15.1.1.7]).

64 Added that urine dipstick pregnancy test is required at this visit per Amendment 2 (Section 15.1.1.18)

65 Post-injection ocular assessments for subjects in the extended dosing group who receive study medication at this visit added per Amendment 2 (Section 15.1.1.22)

9.3 Population characteristics

9.3.1 Demographic

The following demographic parameters will be recorded:

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

9.3.2 Medical/surgical and ophthalmic 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 before signing of the informed consent
- Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

In addition, a complete ophthalmic history will be obtained to check the first set of in- and exclusion criteria as defined in Sections 6.1.1 and 6.2.1 respectively. To this end, the subjects must provide informed consent to allow review of medical records from the time of first aflibercept treatment. The medical records must be sufficient to allow confirmation of eligibility.

9.4 Efficacy

9.4.1 Ophthalmic examinations

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

All ophthalmic evaluations will be conducted according to the schedule detailed in Section 9.1 (Table 9–1).

9.4.1.1 Best corrected visual acuity - amended

Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985) at starting at 4 meters. Visual Acuity (VA) examiners must be certified to ensure consistent measurement of BCVA.[66]

9.4.1.2 Optical coherence tomography (OCT) – amended

Retinal and lesion characteristics will be evaluated using OCT. OCT-images of the study eye and fellow eye will be captured, transmitted to, and read by the independent reading center. All OCTs will be electronically archived at the study sites as part of the source documentation. OCT technicians and equipment must be certified by the reading center to ensure consistency and quality in image acquisition.[67]

9.4.1.3 Indirect ophthalmoscopy

Indirect ophthalmoscopy will be performed for both the study eye and fellow eye in a standard way (i.e. usually using a head-mounted light source and a 20 dpt lens).

At visits with study drug administration, pre-injection indirect ophthalmoscopy will be assessed for both the study eye and fellow eye. Post-injection assessments will be carried out in the study eye only.

66 Removed reference to study manual per Amendment 2 (Section 15.1.1.7)

67 Reworded description of OCT per Amendment 2 (Section 15.1.1.24)

9.4.1.4 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 2-3 drops of phenylephrin-tropicamid (or any other mydriatic) applied topically to the eye.

9.4.1.5 Intra-ocular pressure (IOP)

IOP 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.

IOP will be assessed for both the study eye and fellow eye.

At visits with study drug administration, pre-injection IOP will be assessed for both the study eye and fellow eye. Assessment of IOP 30-60 minutes following IVT injection will be carried out in the study eye only.

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

9.4.1.6 Fundus photography (FP) and fluorescein angiography (FA) - amended

The anatomical state of the retinal vasculature of the study eye will be evaluated by funduscopic examination, FP and FA.

The study eye will be the transit eye. For all visits where the funduscopic examination, FP, and FA procedure are scheduled, FP and FA will be performed on both eyes.

Fundus and angiographic images will be sent to an independent reading center where images will be read. All FA and FP images will be archived electronically at the site as part of the source documentation. Although FA is performed on both eyes, only the study eye will be evaluated by the independent reading center. Photographers must be certified by the reading center to ensure consistency and quality in image acquisition.

FP and FA from the screening visit (Visit 1) will be captured and transmitted for both eyes to an independent reading center where images will be read. A formal check will be done and eligibility will be confirmed by the reading center before randomization.

A detailed protocol for FP and FA image acquisition and assessment can be found in the reading center acquisition protocol.[68]

The treating investigator may perform additional FA/FP at other times during the study based on his/her medical judgment and standard of care.[69]

9.4.2 Efficacy variables

All efficacy variables derived from the ophthalmic examinations are specified in Section 10.3.1.1.

9.5 Pharmacokinetics / pharmacodynamics

not applicable

68 The reading center acquisition protocol will further specify the standards for FA/FP during the study (replaced reference of study manual with reference to reading center acquisition protocol per Amendment 2 [Section 15.1.1.7]).

69 Added requirement to archive FA and FP images electronically, clarified the confirmation of eligibility by the reading center, and re-ordered paragraphs per Amendment 2 (Section 15.1.1.25)

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions - amended

Definition of adverse event (AE)

> 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.[70]

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present at the time of signing the 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 only (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses.

70 Removal of reference to ECG per Amendment 2 (Section 15.1.1.26)

Definition of serious adverse event (SAE)

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 one of the following exceptions is met:

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

   – The admission is pre-planned

   – (e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)

   – The admission is not associated with an AE
   (e.g. social hospitalization for purposes of respite care).

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

d. Results in persistent or significant disability / incapacity

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

e. Is a congenital anomaly / birth defect

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

9.6.1.2 Classifications for adverse event assessment

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

9.6.1.2.1 Seriousness

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

9.6.1.2.2 Intensity

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

- Mild
- Moderate
- Severe

9.6.1.2.3 Causal relationship

In this study, adverse events will be assessed as causally related/not related to (i) the study drug, (ii) IVT injection, and (iii) other protocol-specified procedures. The assessment 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 CRF.

The causal relationship will be recorded using the following terms:

Causal relationship to study drug

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

Causal relationship to the injection procedure

The assessment of a possible causal relationship between the AE and the injection procedure is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no"

- **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.

Causal relationship to other protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no"

- **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 - amended

Any action on study treatment to resolve the AE is to be documented using the categories listed below.[71]

– 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

71 Removal of "Dose reduced" from possible actions taken with study treatment per Amendment 2 (Section 15.1.1.27)

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

The investigator has to record on the respective CRF pages all adverse events (irrespective of any causal relationship or seriousness) occurring in the period between the signing of the informed consent and the end of the 4-weeks period after the last aflibercept injection.

After the end of this period, there is no requirement to actively collect AEs including deaths. For any **drug-related AE** occurring after the end of this period, the standard procedures that are in place for spontaneous reporting will be followed.

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 serious adverse events (SAEs) the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

The means of obtaining information on an AE (e.g. observed, volunteered, or elicited) is to be documented in detail on the eCRF. The following information is required to be recorded:

- The specification of the adverse event
- The date of onset
- The maximum intensity
- Any study drug action and other action taken by the investigator to resolve the adverse events
- Any specific drug or non-drug treatment of the adverse event

- The drug relationship of the adverse event to aflibercept, the IVT injection, or other protocol-specified procedures
- The outcome of the adverse event (for definitions, see above).
- If recovered/resolved or fatal – the date ended.

9.6.1.4 Reporting of serious adverse events

The definition of serious adverse events (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.

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.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the CRF as well as the complementary pages provided in the Investigator File must be completed for each SAE. Information not available at the time of the initial report must be documented on a follow-up SAE form. The sponsor or designee may request substantiating data such as relevant hospital or medical records, diagnostic test reports, and death or autopsy reports.

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

Notification of the IECs / 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 - amended

Information on AEs with an onset after the first application of the test drug is provided in the local label.[72]

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.6.2 Pregnancies - amended

The investigator must report to the sponsor any pregnancy occurring in a female study subject during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

The child's health should be followed up until three months after birth.

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.

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

Results from animal studies with high systemic exposure indicate that aflibercept can impair male and female fertility. Such effects are not expected after ocular administration with very low systemic exposure.[73]

9.6.3 Further safety

9.6.3.1 Laboratory evaluations - amended

Laboratory evaluation will be conducted according to the schedule provided in Section 9.1 (beyond that schedule, pregnancy tests are to be done in women of childbearing potential as frequently as outlined in Table 9–1).[74]

Blood will be drawn before FA by direct venipuncture.[75]

Safety laboratory parameters to be evaluated are summarized in Table 9–2.

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72 Reference to summary of product characteristics replaced with reference to local label for information on AEs per Amendment 2 (15.1.1.28).

73 New paragraph on fertility and guidance regarding the follow-up after birth per Amendment 2 (Section 15.1.1.29)

74 Specification and timing of pregnancy test changed per Amendment 2 (Sections 15.1.1.17 and 15.1.1.18, respectively).

75 Clarification of time point of blood withdrawal with respect to FA per Amendment 2 (Section 115.1.1.30)

The exact date and time (24-hour clock) of each blood sample obtained will be recorded on the appropriate eCRF page. All laboratory tests will be performed at a central laboratory. A copy of the results will be filed in the source documentation.

Table 9–2: Laboratory safety parameters

Chemistry	**Urinalysis**	**Hematology**
Sodium	Glucose	Hemoglobin
Potassium	Protein	Hematocrit
Chloride	Specific Gravity	Red blood cell count
Calcium	Blood	Mean corpuscular volume (MCV)
Glucose	Ketones	Mean corpuscular hemoglobin concentration (MCHC)
Albumin	Protein:Creatinine Ratio (UPCR)	Mean corpuscular hemoglobin (MCH)
Total Protein, Serum		Leucocyte count
Creatinine		Differential count
Blood urea nitrogen (BUN)	**Coagulation**	Neutrophils
Aspartate aminotransferase (AST)	Prothrombin time (PT)	Lymphocytes
Alanine aminotransferase (ALT)	Partial thromboplastin time (PTT)	Monocytes
Alkaline phosphatase	International normalized ratio (INR)	Basophils
Total bilirubin		Eosinophils
Amylase		Platelet count
Total cholesterol		
HDL cholesterol		
Pregnancy test for women of childbearing potential (see Table 9–1)[76]		

HDL: high-density lipoprotein

According to current International Conference on Harmonisation (ICH) guidelines, deviations from the reference range should be evaluated for clinical significance in each individual case. The reference ranges and the units and methods for all variables will be provided by the central laboratory.

Deviations of laboratory values from the laboratory reference ranges will be flagged on the laboratory print-outs.

9.6.3.2 Physical examination

At Screening (Visit 1), a complete physical examination will be performed. Abnormal findings should be documented on the eCRF as either medical history or adverse event (see Section 9.6.1.1).

76 Specification and timing of pregnancy test changed per Amendment 2 (Sections 15.1.1.17 and 15.1.1.18, respectively).

9.6.3.3 Vital signs (temperature, blood pressure and pulse)

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

9.7 Patient-reported outcome – amended

NEI VFQ-25

Vision-related quality of life will be assessed using the NEI VFQ-25 questionnaire (Section 16.1). This questionnaire will be presented in the local language and should be administered in a quiet room by a person certified to administer this type of questionnaire, preferably before other visit procedures are performed. For subjects unable to read the questionnaire owing to vision impairment, a family member, other legal representative of the subject, study nurse, or study physician may assist the subject in completing the questionnaire. In this case, the name of that person should be documented.[77]

9.8 Appropriateness of procedures / measurements

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

No stratification is planned.

Statistical analysis will be performed using SAS; the version used will be specified in the statistical analysis plan.

77 Documentation of name added per Amendment 2 (Section 15.1.1.31)

10.2 Analysis sets

Populations for analysis will be defined as follows:

The **Full Analysis Set** (FAS) will include all randomized subjects who received any study drug *and* have a baseline BCVA assessment *and* at least one post-baseline BCVA assessment. The FAS will be analyzed as randomized.

The **Per-Protocol Set** (PPS) will include all FAS subjects who have at least one BCVA assessment at Week 36 or later *and* do not have a major protocol deviation. The PPS will be analyzed as randomized.

The **Safety Analysis Set** will include all subjects who receive any study drug under this protocol. The safety analysis set will be analyzed as randomized.

10.3 Variables and planned statistical analyses

10.3.1 Variables

10.3.1.1 Efficacy variables

The efficacy variables and the ranking of their statistical analyses at the different timepoints (primary, [key] secondary, exploratory) are specified in Table 10–1. A complete list of variables to be analyzed for this study will be provided in the statistical analysis plan (SAP).

Table 10–1: Efficacy variables

Variable	Ranking	
	Week 52	Week 76
Change from baseline in ETDRS BCVA letter score for the study eye	Primary	Exploratory
Proportion of subjects maintaining vision (i.e. loss of <15 letters) in the study eye	Key secondary	Exploratory
Proportion of subjects who gained from baseline ≥5 letters in the study eye	Secondary	Exploratory
Mean change from baseline in CRT in the study eye	Secondary	Exploratory
Mean change from baseline in CNV area in the study eye	Secondary	Exploratory
Proportion of subjects who lost ≥30 letters	Secondary	Exploratory
Mean change from baseline in total score for NEI VFQ-25	Secondary	Exploratory
Proportion of subjects for whom the treatment interval was extended	Exploratory	Exploratory
Total number of intravitreal injections required in the study eye	Exploratory	Exploratory

BCVA: best corrected visual acuity; CNV: choroidal neovascularization; CRT: central retinal thickness; ETDRS: Early Treatment Diabetic Retinopathy Study; NEI VFQ-25: National Eye Institute 25-item Visual Function Questionnaire

10.3.1.2 Safety variables

The following safety variables will be assessed:

- Adverse events
- Intra-ocular pressure (IOP)
- Body temperature
- Blood pressure
- Pulse
- Laboratory evaluations

Ophthalmic safety evaluations are specified in Section 9.4.1

10.3.2 Statistical and analytical plans

10.3.2.1 Demography and baseline characteristics

Demographic variables and baseline characteristics will be summarized by treatment group and all treatment groups combined for all three analysis populations, depending on the type of data as described in Section 10.1. Medical history will be coded by MedDRA codes and prior and concomitant medications by ATC codes (WHODD). The total score and sub-scores of the NEI VFQ-25 will be calculated according to the NEI VFQ-25 scoring algorithm, August 2000 version.

The treatment group comparability will be checked for each of the analysis populations mentioned above. This comparison will be done with respect to age, baseline BCVA letter score, baseline NEI VFQ-25 total score, and baseline retinal thickness by a one-way analysis of variance main effect model with treatment group as fixed factor. Furthermore, treatment groups will be compared with respect to sex by a Chi-squared test.

The number of injections will be tabulated in both treatment groups. The injection data will be tabulated in more detail for the extended-dosing group (as specified in the SAP).

10.3.2.2 Efficacy analyses – amended

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

Statistical testing will be conducted to prove the non-inferiority of the extended-dosing regimen to the 2Q8 fixed dosing regimen.

The corresponding null hypothesis is H_0: $\mu 1 \leq \mu 2\text{-}D$ versus

the alternative hypothesis H_1: $\mu 1 > \mu 2\text{-}D$, where

D = non-inferiority margin

μi = mean change in BCVA letter score for the study eye from baseline to Week 52 in treatment group i.

i = 1: extended-dosing regimen
2: fixed-dosing regimen

The non-inferiority margin is 5 letters.

The methodological approach will be the calculation of two-sided 95% confidence intervals for the difference in the least squares (LS) means (extended-dosing group minus 2Q8 group) of the change in ETDRS letter score from study baseline to 52 weeks based on a one-way analysis of covariance (ANCOVA) with baseline measure as a covariate and treatment group as a fixed factor (LOCF will be used for missing values at 52 weeks[78]). The extended-dosing regimen will be considered to be non-inferior to the fixed 2Q8 regimen if the confidence interval of the difference lies entirely above -5 letters, where a positive difference favors extended dosing. A non-inferiority margin of 5 letters is consistent with margin used in the "CATT Study" (CATT Research Group 2011).

If, and only if, the extended-dosing regimen is statistically be proven to be non-inferior to the fixed 2Q8 regimen in the primary efficacy analysis, confirmatory testing will be continued to prove the non-inferiority of extended dosing to fixed 2Q8 with regard to the key secondary efficacy variable (maintenance of vision) in the FAS (with LOCF for missing 52-week ETDRS letter score).

78 LOCF is considered an appropriate method for replacement of missing values in the primary and secondary efficacy analyses in the late phase of the study (i.e. carrying forward the last measurement taken between Week 36 to Week 48 if the Week-52 measurement is missing), even though nAMD is a progressive disease.

The null hypothesis is H_0: p1 ≤ p2-Δ versus

the alternative hypothesis H_1: p1 > p2-Δ, where

pi = proportion of subjects maintaining vision at 52 weeks of treatment group i

Δ = pre-specified non-inferiority margin of 7%.[79]

i = 1: extended-dosing regimen
2: fixed-dosing regimen

The methodological approach will be the calculation of two-sided 95% confidence intervals using normal approximation of the difference between the proportions (extended-dosing group minus 2Q8 group) of subjects maintaining vision. The extended-dosing regimen will be considered to be non-inferior to the fixed 2Q8 regimen if the confidence interval of the difference lies entirely above -7%, where a positive difference favors extended dosing. This conditional sequence of statistical hypotheses (a-priori ordered hypotheses) will control for multiplicity in the confirmatory analyses.

As sensitivity analyses, the primary efficacy and key secondary efficacy analyses will be repeated on the Per-Protocol Set as defined in Section 10.2.

The analysis can also include, if applicable, BCVA evolution over the course of pre-study aflibercept treatment, starting with the initial BCVA value as captured in the first set of inclusion criteria. Snellen-equivalents may therefore be converted into ETDRS letter scores.[80]

The other secondary efficacy variables as well as the exploratory efficacy variables will be analyzed in a descriptive manner. This may include 95 % confidence intervals for treatment differences in an exploratory way.

Details regarding the statistical analysis of the other efficacy variables will be provided in the SAP.

10.3.2.3 Safety variables analysis

The safety analysis will be conducted in the safety analysis set. Treatment-emergent AEs will be presented by MedDRA preferred term within primary system organ class (SOC) and summarized by treatment groups. Intensity and causal relationship to the investigational product will be analyzed descriptively. SAEs, including narratives, will be documented separately.

Other safety variables (e.g. IOP measurements, vital signs and laboratory tests) will be analyzed descriptively including changes from baseline. The descriptive analysis of laboratory data will include a listing of laboratory data that fall outside of normal range, and the

79 The non-inferiority margin of 7% was proposed by the 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 pages 22 and 23).

80 Added example of possible analysis per Amendment 2 (Section 15.1.1.35)

calculation of incidence rates for treatment emergent laboratory abnormalities by treatment group.

10.4 Determination of sample size

Based on the assumptions of (i) a standard deviation of 13 for the mean change in BCVA from study baseline to Week 52, (ii) a non-inferiority margin of 5 letters, (iii) an equal mean change in BCVA from study baseline to Week 52 in the two treatment groups, (iv) a power of 90%, and (v) a one-sided alpha of 2.5%, the samples size estimation resulted in 144 evaluable subjects per treatment group (calculated with PASS 11, non-inferiority of two means). With an expected drop-out rate of 13%, a total of 330 subjects should be randomized (165 per treatment group) to ensure the power also in the PPS analysis.

The sample size of 144 evaluable subjects per treatment group will have, in the analysis of the key secondary efficacy variable, power of 0.78 with an assumed proportion of 95% of subjects maintaining vision at Week 52 in both treatment groups, and a power of 0.86 with an assumed proportion of 96% of subjects maintaining vision at Week 52 in both treatment groups (with a two-sided alpha of 5% and a non-inferiority margin of 7%, calculated with PASS 11, non-inferiority of two proportions [differences]).

10.5 Planned interim analyses

Not applicable – no interim analysis is planned.

11. Data handling and quality assurance

11.1 Data recording

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

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 has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer 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 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 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 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 key data entered into the CRF has source documentation available at the site.

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 CRF:

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

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the CRF 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 - amended

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 CRF as well as for data from other sources (e.g. IVRS, laboratory, reading center, adjudication committees).[81]

For data coding (e.g. AEs, medication, surgeries), internationally recognized and accepted dictionaries will be used.[82]

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.

Moreover, the risk of missing data may be decreased in this study, since all subjects must have been treated with the study drug aflibercept for one year to be enrolled in this study and all subjects will receive active aflibercept during the course of this 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.

81 Removal of reference to ECG per Amendment 2 (Section 15.1.1.26)

82 Changed examples per Amendment 2 (Section 15.1.1.32)

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.

Patient (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 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 any interim analysis
  - 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.

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

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

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

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

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

Central reading center for images

An independent central reading center will evaluate the ophthalmic images obtained by OCT (see Section 9.4.1.2) and FP / FA (see Section 9.4.1.6).

External data evaluation bodies

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

In addition, a Safety Management Team (SMT), led by the sponsor's Global Safety Leader, will meet periodically to review safety data. Members of the SMT can include representatives from Global Pharmacovigilance, Pharmacoepidemiology, Clinical Development, Biostatistics, Data Management, Clinical Pharmacology, Preclinical Development, Regulatory Affairs, and Medical Affairs as appropriate.

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

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 Good Clinical Practice (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 - amended

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form 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 9.2.6 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 statistical analysis plan.
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The subject has the right to object to the generation and processing of this post-withdrawal data.[83]

Each subject will have ample time and opportunity to ask questions.

Only if the subject voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The subject / legal representative or proxy consenter 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 patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline 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 unable to read the informed consent form due to vision impairment, a family member, other legal representative of the subject, study nurse, or study physician should read the document verbatim to the subject. A discussion and explanation, including answering all questions from the subject, should also occur prior to the subject or their legal representative signing the form. An impartial witness should be present during the entire informed consent discussion. The witness must be unaffiliated with the conduct of the study, and will also sign and date the document along with the subject or their legal representative. [83]

The informed consent form 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 informed consent form. 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 informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

83 Paragraph revised to align with sponsor internal standards per Amendment 2 (Section 15.1.1.33)

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.

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

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

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

13.6 Compensation for health damage of subjects / insurance

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

13.7 Confidentiality

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

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the CRF, 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

Aiello LP, Avery RL, Arrigg PG et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N Eng J Med 1994; 331:1480-1487.

Rahmani B, Tielsch JM, Katz J et al. The cause-specific prevalence of visual impairment in an urban population. The Baltimore Eye Survey. Ophthalmology. 1996; 103:1721-1726.

The CATT Research Group. Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration. N Eng J Med 2011; 365:1897-1908.

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 2, dated 10 December 2015

15.1.1 Overview of changes to the study

15.1.1.1 Modification 1 – Update of approval status

Update of approved indications for aflibercept by country

Rationale: Update

The following protocol sections are affected by this modification:

- Section 3.1 Background

15.1.1.2 Modification 2 – Clarification of duration of the periods

Clarification of the duration of the screening period (change from expression in weeks to expression in days) and other periods

Rationale: Clarification

The following protocol sections are affected by this modification:

- Synopsis – Study design
- Section 5 Study design
- Section 9 Procedures and variables
- Section 9.1 Tabular schedule of evaluations
- Section 9.2.1 Screening visit (Visit 1)

15.1.1.3 Modification 3 – Time windows and schedule of visits

Consistency throughout the protocol: Different time windows (± 3 and ± 7 days given at different protocol sections) were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline and clarification of the schedule of visits in the 2Q8 group.

Rationale: Clarification and consistency

The following protocol sections are affected by this modification:

- Synopsis – Test drugs – Doses
- Synopsis – Study design
- Section 5 Study design
- Section 7.1 Treatments to be administered
- Section 9 Procedures and variables
- Section 9.1 Tabular schedule of evaluations

15.1.1.4 Modification 4 – Selection of study eye

Clarification of the procedure of selecting the study eye

Rationale: Clarification

The following protocol sections are affected by this modification:

- Section 6 Study population

15.1.1.5 Modification 5 – Clarifications of inclusion criteria

Clarified the following in the first and second set of inclusion criteria:

- FA is sufficient for inclusion criterion 1 - removal of FP (inclusion criterion 1)
- Clarification of the conversion from BCVA to letter score (inclusion criterion 3)
- 'Written informed consent' complemented by 'signed' (Inclusion criterion 4)
- Clarification of timepoint of the last allowed aflibercept injection before first treatment in the study

Rationale: Clarification

The following protocol sections are affected by this modification:

- Synopsis – Diagnosis and main criteria for inclusion / exclusion
- Section 6.1 Inclusion criteria

15.1.1.6 Modification 6 – Time periods for inclusion criteria 1 and 2

Extension of the time periods from 3 weeks to 4 weeks

Rationale: Update to reflect clinical practice

The following protocol sections are affected by this modification:

- Section 6.1 Inclusion criteria
- Synopsis – Diagnosis and main criteria for inclusion / exclusion

15.1.1.7 Modification 7 – Study manual

Removed references to study manual and added references to reading center acquisition protocol for FA and FP

Rationale: Correction

The following protocol sections are affected by this modification:

- Synopsis – Diagnosis and main criteria for inclusion / exclusion
- Section 6.1 Inclusion criteria
- Section 9.2.1 Screening visit (Visit 1)

- Section 9.2.4 Primary completion (Week 52)
- Section 9.4.1.1 Best corrected visual acuity
- Section 9.4.1.6 Fundus photography (FP) and fluorescein angiography (FA)

15.1.1.8 Modification 8 – Inclusion criterion 8

Use of contraception specified according to the recommendations of the CTFG from 15 SEP 2014.

Rationale: For subject safety reasons

The following protocol sections are affected by this modification:

- Section 6.1.2 Second set of inclusion criteria

15.1.1.9 Modification 9 – Clarifications in second set of exclusion criteria

Clarifications added

Rationale: Clarification

The following protocol sections are affected by this modification:

- Section 6.2.2 Second set of exclusion criteria

15.1.1.10 Modification 10 – Re-screening criteria

Added list of criteria for re-screening

Rationale: Correction (omission in the original protocol)

The following protocol sections are affected by this modification:

- Section 6.3.1 Withdrawal

15.1.1.11 Modification 11 – Subject identification number

Description of subject identification number changed

Rationale: Correction

The following protocol sections are affected by this modification:

- Section 6.4 Subject identification

15.1.1.12 Modification 12 – Identity of study drug

Added table specifying the identity of study drug

Rationale: Correction (omission in the original protocol)

The following protocol sections are affected by this modification:

- Section 7.2 Identity of study drug

15.1.1.13 Modification 13 – EU SmPC and other updates for safety reasons to dosage and administration

Special warnings from EU Summary of product characteristics (SmPC) (most recent version number) added to dosage and administration and dosage and administration updated

Rationale: For subject safety reasons

The following protocol sections are affected by this modification:

- Section 7.4 Dosage and administration

15.1.1.14 Modification 14 – Treatment posology

Added table describing treatment posology

Rationale: Clarification

The following protocol sections are affected by this modification:

- Section 7.4 Dosage and administration

15.1.1.15 Modification 15 – Drug storage

Added description of storage conditions

Rationale: More detailed specification

The following protocol sections are affected by this modification:

- Section 7.6 Drug logistics and accountability

15.1.1.16 Modification 16 – Final visit or early termination visit

Clarified throughout the protocol that the final visit procedures should also be conducted in the case of early termination and changed end of study visit to final visit

Rationale: Clarification

The following protocol sections are affected by this modification:

- Section 8.1.2.1 Study-eye treatment
- Section 9 Procedures and variables
- Section 9.1 Tabular schedule of evaluations
- Section 9.2.5 Visits between primary completion (Week 52) and end of study visit (Week 76)
- Section 9.2.6 End of study (Week 76)

15.1.1.17 Modification 17 – Specification of pregnancy testing

Added a urine dipstick pregnancy test to the baseline visit

Rationale: A patient could become pregnant between screening and baseline. To confirm that the subject is not pregnant before the start of treatment, a urine dipstick pregnancy test is to be performed at the baseline visit.

The following protocol sections are affected by this modification:

- Section 9.1 Tabular schedule of evaluations
- Section 9.2.2 Baseline visit (Visit 2)
- Section 9.6.3.1 Laboratory evaluations

15.1.1.18 Modification 18 – Timing of pregnancy testing

Moved the serum pregnancy test in the Schedule of assessments and study procedures from Initiation procedures to Standard safety. Added foot note ‘The urine dipstick pregnancy test is to be repeated as frequently as required following the investigator’s medical judgment and local regulations’ to the Tabular schedule of evaluations. Added that a urine dipstick pregnancy test is required at the final visit or early termination.

Rationale: For subject safety reasons

The following protocol sections are affected by this modification:

- Section 9.1 Tabular schedule of evaluations
- Section 9.2.6 End of study visit (Week 76)
- Section 9.6.3.1 Laboratory evaluations

15.1.1.19 Modification 19 – Order of footnotes and minor clarifications in schedule of evaluations

Arranging the footnotes in the order the table is read, line by line, and separated the table to 2 pages; and minor clarifications regarding pre-and post-dose assessments for indirect ophthalmoscopy and IOP

Rationale: More reader friendly

The following protocol sections are affected by this modification:

- Section 9.1 Tabular schedule of evaluations

15.1.1.20 Modification 20 – Removal of sample study drug injection protocol from appendix

Removed sample study drug injection protocol (Drug administration protocol) from the appendix

Rationale: Harmonization with other post-authorization efficacy studies

The following protocol sections are affected by this modification:

- Section 7.4 Dosage and administration
- Section 9.1 Tabular schedule of evaluations
- Appendix 16.1 Drug administration protocol

15.1.1.21 Modification 21 – Re-check of eligibility criteria

Clarified the re-check of inclusion and exclusion criteria at the Baseline visit

Rationale: Clarification

The following protocol sections are affected by this modification:

- Section 9.2.2 Baseline Visit (Visit 2)

15.1.1.22 Modification 22 – Post-injection ocular assessments

Added post-injection ocular assessments to all treatment visits

Rationale: Clarification (omitted in some sections in the original protocol)

The following protocol sections are affected by this modification:

- Section 9.2.2 Baseline Visit (Visit 2)
- Section 9.2.3 Visits between baseline and Week 52
- Section 9.2.4 Primary completion (Week 52)

- Section 9.2.5 Visits between primary completion (Week 52) and end of study (Week 76)
- Section 9.2.6 End of study (Week 76)

15.1.1.23 Modification 23 – Conduct of visits

Added the full list of study procedures to the visits between primary completion (Week 52) and the final visit (Week 76) or early termination instead of a reference only

Rationale: More reader friendly

The following protocol sections are affected by this modification:

- Section 9.2.5 Visits between primary completion (Week 52) and end of study (Week 76)
- Section 9.2.6 End of study (Week 76)

15.1.1.24 Modification 24 – OCT

Reworded description of OCT in efficacy section

Rationale: Harmonization with other post-authorization efficacy studies

The following protocol sections are affected by this modification:

- Section 9.4.1.2 Optical coherence tomography (OCT)

15.1.1.25 Modification 25 – FA and FP

Added requirement to archive FA and FP images electronically, clarified the confirmation of eligibility by the reading center, and re-ordered paragraphs

Rationale: Clarification and more reader friendly

The following protocol sections are affected by this modification:

- Section 9.4.1.6 Fundus photography (FP) and fluorescein angiography (FA)

15.1.1.26 Modification 26 – ECG

Removal of references to electrocardiogram (ECG)

Rationale: Correction

The following protocol sections are affected by this modification:

- Section 9.6.1.1 Definitions
- Section 11.3 Data processing

15.1.1.27 Modification 27 – Actions taken with study treatment

Removal of "Dose reduced" from possible actions taken with study treatment

Rationale: Correction

The following protocol sections are affected by this modification:

- Section 9.6.1.2.4 Action taken with study treatment

15.1.1.28 Modification 28 – Expected adverse events

Reference to summary of product characteristics replaced with reference to local label for information on AEs.

Rationale: Editorial clarification of the process

The following protocol sections are affected by this modification:

- Section 9.6.1.5 Expected adverse events

15.1.1.29 Modification 29 – Pregnancies

New paragraph on fertility and guidance regarding the follow-up after birth added to the pregnancy section

Rationale: Addition of guidance

The following protocol sections are affected by this modification:

- Section 9.6.2 Pregnancies

15.1.1.30 Modification 30 – Time point of blood withdrawal

Clarification of time point of blood withdrawal with respect to FA

Rationale: Clarification

The following protocol sections are affected by this modification:

- Section 9.6.3.1 Laboratory evaluations

15.1.1.31 Modification 31 – NEI VFQ-25 questionnaire

Requirement to document the name of the person assisting the subject in completing the NEI VFQ-25 questionnaire added.

Rationale: Clarification of process

The following protocol sections are affected by this modification:

- Section 9.7 Patient-reported outcome - NEI VFQ 25

15.1.1.32 Modification 32 – Data processing

Minor rewording (changed examples)

Rationale: Clarification

The following protocol sections are affected by this modification:

- Section 11.3 Data processing

15.1.1.33 Modification 33 – Subject information and consent process

Revision of text describing the subject information and informed consent process

Rationale: Alignment with sponsor internal standards

The following protocol sections are affected by this modification:

- Section 13.4 Subject information and consent

15.1.1.34 Modification 34 – Fellow eye treatment

Added possibility to treat the fellow eye with any local standard of care

Rationale: More detailed specification

The following protocol sections are affected by this modification:

- Section 8.1.2.2 Fellow eye treatment

15.1.1.35 Modification 35 – Efficacy analyses – sensitivity analyses

Added example of possible analysis

Rationale: More detailed specification

The following protocol sections are affected by this modification:

- Section 10.3.2.2 Efficacy analyses

15.1.2 Changes to the protocol text

Changes to the protocol text are highlighted as specified at the beginning of Section15.

Changes to abbreviations (i.e. the location where the abbreviation is first used changed) are not highlighted.

Synopsis – Test drugs – Doses

Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline per Modification 3 (Section 15.1.1.3)

Old text:

Dose(s)	Test group:	2 mg with flexible injection intervals (≥ 8 weeks) (extended-dosing regimen)
	Control group:	2 mg with fixed injection intervals (8 weeks ~~± 7 days~~) (2Q8)

New text:

Dose(s)	Test group:	2 mg with flexible injection intervals (≥ 8 weeks) (extended-dosing regimen)
	Control group:	2 mg with fixed injection intervals (8 weeks) (2Q8)

Synopsis – Diagnosis and main criteria for inclusion / exclusion

Clarifications in the inclusion criteria per Modification 5 (Section 15.1.1.5)

Extension of the time periods from 3 weeks to 4 weeks for the first 2 criteria of the first set of inclusion criteria per Modification 6 (Section 15.1.1.6)

Removed references to study manual (Section 15.1.1.7)

Old text:

Diagnosis and main criteria for inclusion / exclusion	**First set** of inclusion criteria: The following criteria must have been met at the initial start of aflibercept treatment (i.e. start of aflibercept treatment before this study): • Subject had primary subfoveal choroidal neovascularization (CNV) lesions secondary to nAMD, including juxtafoveal lesions that affect the fovea, as evidenced by fluorescein angiography/~~photography~~ (FA/~~FP~~) of the study eye within ~~3~~ weeks before the initiation of aflibercept treatment. • The area of CNV occupied at least 50% of the total lesion within ~~3~~ weeks before the initiation of aflibercept treatment. • Documented best-corrected visual acuity (BCVA) was 20/40 to 20/320 (letter score of 73 to 25) in the study eye at the initiation of treatment. ~~Because BCVA may not have been assessed by the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, guidance for conversion of Snellen visual acuity assessments will be provided in the study manual.~~

New text:

Diagnosis and main criteria for inclusion / exclusion	**First set** of inclusion criteria: The following criteria must have been met at the initial start of aflibercept treatment (i.e. start of aflibercept treatment before this study): • Subject had primary subfoveal choroidal neovascularization (CNV) lesions secondary to nAMD, including juxtafoveal lesions that affect the fovea, as evidenced by fluorescein angiography (FA) of the study eye within 4 weeks before the initiation of aflibercept treatment. • The area of CNV occupied at least 50% of the total lesion within 4 weeks before the initiation of aflibercept treatment. • Documented best-corrected visual acuity (BCVA) was 20/40 to 20/320 (comparable to a letter score of 73 to 25) in the study eye at the initiation of treatment (the initial BCVA of the study eye before treatment initiation must be documented as Snellen equivalent in the electronic case report form [eCRF]).

Synopsis – Study design

Clarification of the period durations per Modification 2 (Section 15.1.1.2)

Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline per Modification 3 (Section 15.1.1.3)

Old text:

This study comprises a screening period of up to ~~8 weeks (+ 10 days) and a treatment period of 72 weeks (up to 76 weeks in the extended dosing group). A final study visit for all subjects will be conducted at Week 76.~~

…

2Q8: Fixed dosing intervals
8 weeks ~~(±7 days)~~ - modification of the treatment interval is not allowed.

Subjects in both treatment groups will receive the first study treatment on Day 1. The treatment period is 72 weeks (~~or up to 76 weeks in the extended dosing group~~) with a final study visit at Week 76.

New text:

This study comprises a screening period of up to 66 days.

…

2Q8: Fixed dosing intervals
8 weeks - modification of the treatment interval is not allowed.

For each treatment group, the time window for all post-baseline visits is ± 3 days relative to baseline.

Subjects in both treatment groups will receive the first study treatment on Day 1. The treatment period is 72 weeks (in the 2Q8 group) with a final study visit at Week 76

Section 3.1 Background

Update of approved indications for aflibercept by country per Modification 1 (Section 15.1.1.1)

Old text:

… ~~To date, aflibercept has been approved as a treatment for nAMD in the United States (US), European Union (EU), Japan and several other countries and for the treatment of macular edema secondary to central retinal vein occlusion (CRVO) in the US and several other countries. Phase 3 studies of aflibercept in diabetic macular edema (DME), branch retinal vein occlusion (BRVO), and myopic choroidal neovascularization (mCNV) are ongoing.~~

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

New text:

… To date, aflibercept has been approved as a treatment for nAMD, macular edema secondary to central retinal vein occlusion (CRVO), diabetic macular edema (DME), and macular edema secondary to branch retinal vein occlusion (BRVO) and CRVO in the United States (US), European Union (EU), Japan, and other countries; as well as for myopic choroidal neovascularization (mCNV) in the EU, Japan and other countries; and for diabetic retinopathy in patients with DME in the US.

Section 5 Study design

Clarification of the period durations per Modification 2 (Section 15.1.1.2)

Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline per Modification 3 (15.1.1.3).

Old text:

This study comprises a screening period of up to ~~8 weeks (+ 10 days) and a treatment period of 72 weeks (up to 76 weeks in the extended-dosing group)~~ (Figure 5-1).

There will be two parallel treatment arms. In both arms, aflibercept will be injected IVT at a dose of 2 mg per injection. The treatment arms differ in dosing intervals:

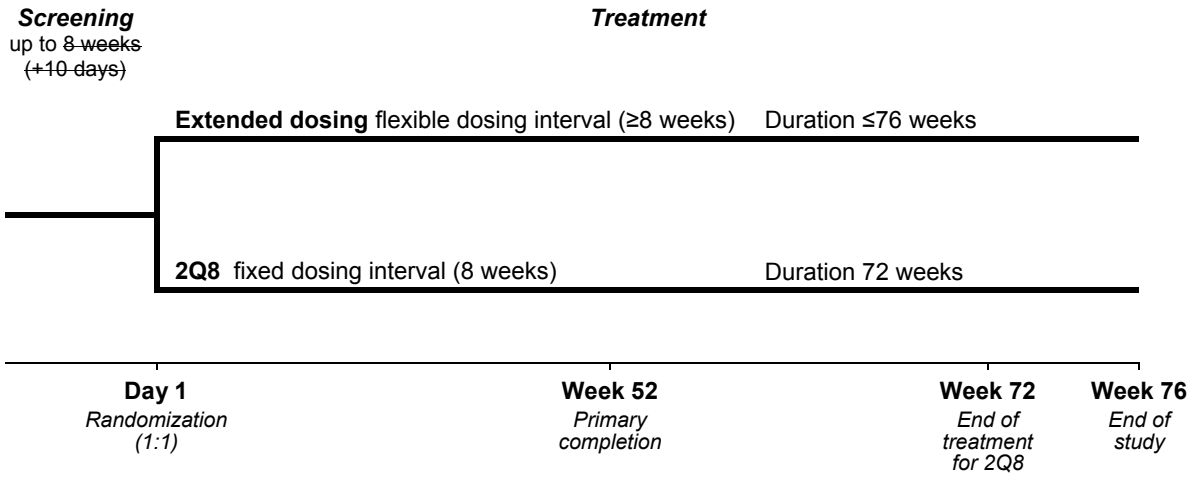
Extended dosing: Flexible dosing intervals

≥8 weeks (no upper limit) based on visual and anatomic outcomes as judged by the investigator.

When/if visual and 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 were observed).

2Q8: Fixed dosing intervals
8 weeks ~~(±7 days)~~ - modification of the treatment interval is not allowed.

Figure 5-1: Study flow diagram



Following screening, eligible subjects will be randomized (1:1) to one of the two parallel treatment group. Subjects in both treatment groups will receive the first study treatment on Day 1. The treatment period is 72 weeks (~~or up to 76 weeks in the extended-dosing group~~) with a final study visit at Week 76.

~~Two post-baseline visits will follow the same strict schedule in both treatment groups: primary completion at Week 52 and the final visit at Week 76. All other post-baseline visits may differ between the treatment groups as detailed in Section 9.~~

The last possible study drug injection in the extended-dosing group can be given at Week 76 (i.e. the end of the study) after completion of all protocol-specified assessments. After Week 76, subjects should be returned to standard of care.

New text:

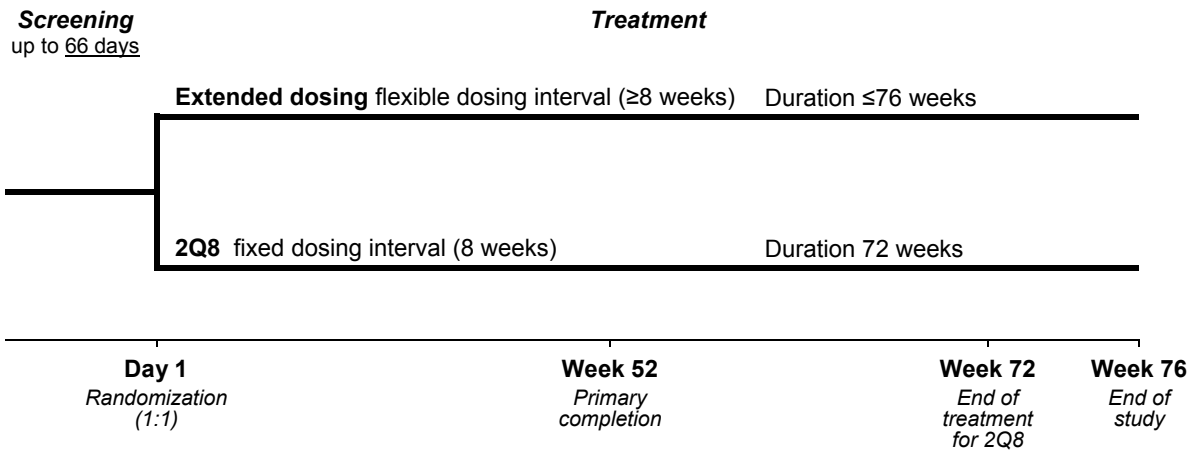
This study comprises a screening period of up to 66 days (Figure 5-1).

There will be two parallel treatment arms. In both arms, aflibercept will be injected IVT at a dose of 2 mg per injection. The treatment arms differ in dosing intervals:

Extended dosing: Flexible dosing intervals
≥8 weeks (no upper limit) based on visual and anatomic outcomes as judged by the investigator.
When/if visual and 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 were observed).

2Q8: Fixed dosing intervals
8 weeks - modification of the treatment interval is not allowed.

Figure 5-1: Study flow diagram - amended



Following screening, eligible subjects will be randomized (1:1) to one of the two parallel treatment group. Two post-baseline visits will follow the same strict schedule in both treatment groups: primary completion at Week 52 and the final visit at Week 76. The schedule of all other post-baseline visits may differ between the treatment groups as detailed in Section 9.

Subjects in both treatment groups will receive the first study treatment on Day 1. The treatment period is 72 weeks (in the 2Q8 group) with a final study visit at Week 76.

The last possible study drug injection in the extended-dosing group can be given at Week 76 (i.e. the end of the study) after completion of all protocol-specified assessments. After Week 76, subjects should be returned to standard of care.

For each treatment group, the time window for all post-baseline visits is ± 3 days relative to baseline.

Section 6 Study population

Clarification of the procedure of selecting the study eye per Modification 4 (Section 15.1.1.4)

Old text:

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 (VA) will be selected as the study eye. If both eyes have equal VA, 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.

New text:

Only one eye will be designated as the study eye. For subjects who meet eligibility criteria in both eyes during the screening phase, the eye with the worse visual acuity (VA) will be selected as the study eye. If both eyes have equal VA, 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.

Section 6.1 Inclusion criteria

Clarifications in the first and second set of inclusion criteria per Modification 5 (Section 15.1.1.5)

Extension of the time periods from 3 weeks to 4 weeks for inclusion criteria 1 and 2 per Modification 6 (Section 15.1.1.6)

Removed reference to study manual per Modification 7 (Section 15.1.1.7)

Use of contraception specified according to the recommendations of the CTFG per Modification 8 (Section 15.1.1.8)

Old text:

Section 6.1.1 First set of inclusion criteria

All of the following criteria must have been met at the initial start of aflibercept treatment (i.e. start of aflibercept treatment prior to this study) for a subject to be eligible for this study.

1. Subject had primary subfoveal choroidal neovascularization (CNV) lesions secondary to nAMD, including juxtafoveal lesions that affect the fovea, as evidenced by FA~~/FP~~ of the study eye within ~~3~~ weeks before the initiation of aflibercept treatment.[84]
2. The area of CNV occupied at least 50% of the total lesion within ~~3~~ weeks before the initiation of aflibercept treatment.
3. Documented BCVA was 20/40 to 20/320 (letter score of 73 to 25) in the study eye at the initiation of treatment. ~~Because BCVA may not have been assessed by the ETDRS protocol at initiation of aflibercept treatment, guidance for conversion of data (e.g. Snellen to approximate ETDRS) will be provided in the study manual.~~

Section 6.1.2 Second set of inclusion criteria

All of the following criteria must be met at the time of screening for participation in this study for a subject to be eligible for this study.

4. Written informed consent
5. Men or women ≥ 51 years of age

84 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~~.

6. The subject's history of aflibercept treatment meets ALL of the following:
   a) Treatment in the study eye was initiated with three monthly (-1 week/+2 weeks) doses of 2 mg aflibercept and improvements of visual and anatomic outcomes were observed
   b) Following the above initiation phase, the intervals between treatments were between 6 weeks and 12 weeks (one exception will be allowed)
   c) The interval between the last two pre-study injections was ≥8 weeks, and visual and anatomic outcomes have been stable over this interval.
   d) The subject received the last IVT injection of aflibercept in the study eye ≥2 months (±10 days) before the first treatment in this study
   e) Total prior treatment duration with aflibercept (i.e. from first treatment to randomization into this study) was ≥12 months
7. Subject is willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
~~8. Women and men of reproductive potential must agree to utilize two reliable and acceptable methods of contraception simultaneously when sexually active. This applies for the time period between signing of the informed consent form and 3 months after the last administration of study drug.~~

   ~~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.~~

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

New text:

Section 6.1.1 First set of inclusion criteria

All of the following criteria must have been met at the initial start of aflibercept treatment (i.e. start of aflibercept treatment prior to this study) for a subject to be eligible for this study.

1. Subject had primary subfoveal choroidal neovascularization (CNV) lesions secondary to nAMD, including juxtafoveal lesions that affect the fovea, as evidenced by FA of the study eye within 4 weeks before the initiation of aflibercept treatment.[85]
2. The area of CNV occupied at least 50% of the total lesion within 4 weeks before the initiation of aflibercept treatment.
3. Documented BCVA was 20/40 to 20/320 (comparable to a letter score of 73 to 25) in the study eye at the initiation of treatment (the initial BCVA of the study eye before treatment initiation must be documented as Snellen equivalent in the electronic case report form [eCRF]).

85 The reading center acquisition protocol will further specify the standards for FA during the study.

Section 6.1.2 Second set of inclusion criteria

All of the following criteria must be met at the time of screening for participation in this study for a subject to be eligible for this study.

4. Signed written informed consent
5. Men or women ≥ 51 years of age
6. The subject's history of aflibercept treatment meets ALL of the following:
   a) Treatment in the study eye was initiated with three monthly (-1 week/+2 weeks) doses of 2 mg aflibercept and improvements of visual and anatomic outcomes were observed
   b) Following the above initiation phase, the intervals between treatments were between 6 weeks and 12 weeks (one exception will be allowed)
   c) The interval between the last two pre-study injections was ≥8 weeks, and visual and anatomic outcomes have been stable over this interval.
   d) The subject received the last IVT injection of aflibercept in the study eye 2 months (±10 days) before the first treatment in this study
   e) Total prior treatment duration with aflibercept (i.e. from first treatment to randomization into this study) was ≥12 months
7. Subject is willing, committed, and able to return for ALL clinic visits and complete all study-related procedures.
8. Women and men of reproductive potential must agree to a method of highly effective contraception (as defined by the Clinical Trial Facilitation Group [CTFG] from 15 SEP 2014):
   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
     - oral
     - intravaginal
     - transdermal
   - Progestogen-only hormonal contraception associated with inhibition of ovulation:
     - oral
     - injectable
     - implantable
   - Intrauterine device
   - Intrauterine hormone-releasing system
   - Bilateral tubal occlusion
   - Vasectomized partner
   - Sexual abstinence

   Alternatively women and men of reproductive potential can also use two acceptable methods of contraception (as defined by the CTFG from 15 SEP 2014) simultaneously:
   - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

- Male or female condom with or without spermicide
- Cap, diaphragm or sponge with spermicide

Contraception has to be used from signing the informed consent form until 3 months after the last administration of study drug. Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of child bearing potential.

Section 6.2.2 Second set of exclusion criteria

Clarifications added per Modification 9 (Section 15.1.1.9)

Old text:

…

12. Any vitreous hemorrhage within 4 weeks before randomization
13. Active intraocular, extraocular and periocular inflammation or infection in either eye.
14. Any ocular or periocular infection within 4 weeks of randomization
15. Any serious adverse event related to aflibercept during prior treatment (see Sections 9.6.1.1 and 9.6.1.2)
16. Any history of allergy to povidone iodine
17. Known serious allergy to the fluorescein sodium for injection in angiography
18. Presence of any contraindications indicated in the EU commission/locally approved label for aflibercept: Hypersensitivity to the active substance aflibercept or to any of the excipients; active or suspected ocular or periocular infection; active severe intraocular inflammation
19. Prior vitrectomy in the study eye
20. History of vitreomacular traction

…

33. The use of long acting steroids, either systemically or intraocular, in the 18 months before initiating study treatment

…

New text:

…

12. Any vitreous hemorrhage within 4 weeks before randomization in the study eye
13. Active intraocular, extraocular and periocular inflammation or infection in either eye.
14. Any ocular or periocular infection within 4 weeks of randomization in either eye

15. Any serious adverse event related to aflibercept during prior treatment (see Sections 9.6.1.1 and 9.6.1.2
16. Any history of allergy or hypersensitivity to povidone iodine.
17. Known serious allergy or hypersensitivity to the fluorescein sodium for injection in angiography
18. Presence of any contraindications indicated in the EU commission/locally approved label for aflibercept: Hypersensitivity to the active substance aflibercept or to any of the excipients; active or suspected ocular or periocular infection; active severe intraocular inflammation
19. Prior vitrectomy in the study eye
20. History of vitreomacular traction in the study eye

…

33. The use of long acting steroids, either systemically or intraocular, in the 18 months before initiating study treatment (or Iluvien IVT implant at any time)

…

Section 6.3.1 Withdrawal

Added list of criteria for re-screening per Modification 10 (Section 15.1.1.10)

Old text:

Screening failure

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

New text:

Screening failure

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

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 inclusion / exclusion criteria preventing the subject's initial attempt to participate have been changed (see inclusion criterion 1 and 2 changed via this protocol amendment).

- The reason for the screening failure was subsequently resolved (e.g. elevated IOP decreases, inflammation or infection resolves) 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 has to sign a new informed consent form. To be eligible, re-screened subjects must meet all eligibility criteria during the re-screening period.

Section 6.4 Subject identification

Description of subject identification number changed per Modification 11 (Section 15.1.1.11)

Old text:

The subject number is a 9 digit number consisting of:

~~Digits 1 to 2 = Country code~~

~~Digits 3 to 5 = Center number within the country~~

~~(Digits 1 to 5 = Trial unit)~~

~~Digits 6 to 9 = Current subject number within the center~~

~~The sponsor or designee will provide the centers with a sufficient number of center-specific PIDs to cover all potential subjects.~~ Once allocated, the subject's PID number will identify the subject throughout the study, and will be entered into the Site Enrollment Log and on the eCRF.

New text:

The subject number is a 9 digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current subject number within the center

Patient identification numbers (PIDs) will be assigned via IxRS. Once allocated, the subject's PID number will identify the subject throughout the study, and will be entered into the Site Enrollment Log and on the eCRF.

Upon re-screening, a new PID will be assigned.

Section 7.1 Treatments to be administered

Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline per Modification 3 (Section 15.1.1.3)

Old text:

There will be two parallel treatment arms, each administering 2 mg aflibercept per injection IVT in the study eye. Aflibercept will be administered either on a fixed 2Q8 schedule (i.e. 2 mg aflibercept every 8 weeks ~~[±7 days])~~ or according to an extended-dosing protocol in which the dosing interval may be extended beyond 8 weeks based on visual and anatomical outcomes and knowledge of the individual subject as judged by the treating investigator (Table 7-1).

Table 7-1: Treatment groups

	Extended-dosing group	2Q8 group
Dose per injection	Aflibercept 2 mg	Aflibercept 2 mg
Administration schedule	Flexible injection intervals: ≥8 weeks When/if exudation recurs, the treatment interval will revert to the last treatment interval in which the disease was inactive. Interval decisions based investigator's judgment. Intervals cannot be less than 8 weeks (no upper limit).	Fixed injection intervals: 8 weeks ~~±7 days~~ throughout the entire treatment period
Duration of treatment	up to 76 weeks	72 weeks
Planned number of randomized subjects	165	165

New text:

There will be two parallel treatment arms, each administering 2 mg aflibercept per injection IVT in the study eye. Aflibercept will be administered either on a fixed 2Q8 schedule (i.e. 2 mg aflibercept every 8 weeks) or according to an extended-dosing protocol in which the dosing interval may be extended beyond 8 weeks based on visual and anatomical outcomes and knowledge of the individual subject as judged by the treating investigator (Table 7-1).

Table 7-1: Treatment groups - amended

	Extended-dosing group	2Q8 group
Dose per injection	Aflibercept 2 mg	Aflibercept 2 mg
Administration schedule[a]	Flexible injection intervals: ≥8 weeks When/if exudation recurs, the treatment interval will revert to the last treatment interval in which the disease was inactive. Interval decisions based investigator's judgment. Intervals cannot be less than 8 weeks (no upper limit).	Fixed injection intervals: 8 weeks throughout the entire treatment period
Duration of treatment	up to 76 weeks	72 weeks
Planned number of randomized subjects	165	165

[a] For each treatment group, the time window for all post-baseline visits is ± 3 days relative to baseline

Section 7.2 Identity of study treatment

Following table added specifying the identity of study drug per Modification 12 (Section 15.1.1.12)

The identity of the study drug is summarized in Table 7-2.

Table 7-2: Identity of study drug - added

Name	Dose	Concentration	Formulation	Composition
BAY 86-5321 aflibercept Eylea	2 mg	40 mg/mL	Solution for intravitreal injection	– 40 mg aflibercept/mL – 5% sucrose – 10mM sodium phosphate – 0.03% polysorbate 20 – 40 mM NaCl – Water for injection

Section 7.4 Dosage and administration

Dosage and administration updated and special warnings from EU SmPC (most recent version number) added to dosage and administration per Modification 13 (Section 15.1.1.13)

Added table describing treatment posology per Modification 14 (Section 15.1.1.14)

Removed sample study drug injection protocol from the appendix per Modification 20 (Section 15.1.1.20).

Old text:

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

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

~~Prior to usage, the unopened vial of aflibercept may be stored at room temperature (25°C/77°F) for up to 24 hours. After opening the vial, proceed under aseptic conditions.~~

~~An example of a drug administration protocol is provided in Section 16.1.~~

New text:

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

- Sterile study drug in sealed glass vials (2 mL) with a withdrawable volume of 0.1 mL (see Table 7-2 for details on the composition of the study drug)
- Filter needle (18 gauge)

Other ancillary components required for the administration of aflibercept (e.g. 30-gauge injection needle; 1-ml syringe) will be supplied by the study site.

When aflibercept vials are removed from the refrigerator, the solution should be visually inspected and it should have no evidence of turbidity. If particulates, cloudiness, or discoloration are visible, the vial must not be used.

After opening the vial, all preparation steps have to take place under aseptic conditions.

The study drug will be withdrawn using aseptic technique through the filter needle attached to the 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 by the sterile 30-gauge needle for the IVT injection. Each patient receives an IVT injection of 50 µl of aflibercept.

Consideration of special warnings from EU label

The investigator should consider the special warnings as described in the EU label for aflibercept. However, ultimately the investigator should include in his/her treatment decision all subject related information and data available and based on this decide what would be best for the subject.

The approved EU label for aflibercept includes the following special warnings:

Treatment should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes. In the event of a retinal break, the dose should be withheld and treatment should not be resumed until the break is adequately repaired.

The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of:

- a decrease in BCVA of ≥30 letters compared with the last assessment of visual acuity;
- a subretinal haemorrhage involving the centre of the fovea, or, if the size of the haemorrhage is ≥50%, of the total lesion area

The dose should be withheld within the previous or next 28 days in the event of a performed or planned intraocular surgery

Posology

Treatment posology is detailed in Table 7-3.

Table 7-3: Treatment posology - added

	2Q8 group		Extended-dosing group	
	Visit	Treatment	Visit	Treatment
Baseline	mandatory Visit 2	mandatory	mandatory Visit 2	mandatory
Week 8	mandatory visit with treatment		*between Week 8 and Week 52, visits (including treatment) can be scheduled at any timepoint (provided injection intervals are ≥8 weeks)*	
Week 16	mandatory visit with treatment			
Week 24	mandatory visit with treatment			
Week 32	mandatory visit with treatment			
Week 40	mandatory visit with treatment			
Week 48	mandatory visit with treatment			
Week 52	mandatory	no treatment	mandatory	optional
Week 56	mandatory visit with treatment		*between Week 52 and Week 76, visits (including treatment) can be scheduled at any timepoint (provided injection intervals are ≥8 weeks)*	
Week 64	mandatory visit with treatment			
Week 72	mandatory visit with treatment			
Week 76	mandatory	no treatment	mandatory	optional

Section 7.6 Drug logistics and accountability

Added the following paragraph to 'Storage' per Modification 15 (Section 15.1.1.15):

Aflibercept must be stored at the clinical sites in a refrigerator at 2°C to 8°C, protected from light, and not frozen. Prior to usage, the unopened vial of aflibercept may be stored at room temperature (25 °C / 77°F) for up to 24 hours. After opening the vial or blister pack, proceed under aseptic conditions.

Section 8.1.2.1 Study eye treatment

Clarification that the final visit procedures should also be conducted in the case of early termination per Modification 16 (Section 15.1.1.16)

Old text:

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

New text:

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

Section 8.1.2.2 Fellow eye treatment

Added possibility to treat the fellow eye with any local standard of care per Modification 34 (Section 15.1.1.34)

Old text:

Treatment of the fellow (non-study) eye is not regarded as a study treatment. If the fellow eye has AMD, the fellow eye may receive any locally approved non-systemic treatment. If the fellow eye shall be treated pharmacologically, the most appropriate treatment option that is approved by the governing health authorities may be selected at the investigator's discretion in the subject's best interest.

If it is determined that aflibercept is the most appropriate treatment option for the fellow eye, this will still not be regarded as a study treatment and 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.

New text:

Treatment of the fellow (non-study) eye is not regarded as a study treatment. If the fellow eye has AMD, the fellow eye may receive any locally approved non-systemic treatment. If the fellow eye shall be treated pharmacologically, the most appropriate treatment option that is approved by the governing health authorities may be selected at the investigator's discretion in the subject's best interest.

If no drug therapy has been approved for the indication or if the approved therapy is not appropriate due to medical reasons, a non-approved pharmacological approach may be selected, if it can be considered as local standard of care.

If it is determined that aflibercept is the most appropriate treatment option for the fellow eye, this will still not be regarded as a study treatment and 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.

Section 9 Procedures and variables

Clarification of the period durations per Modification 2 (Section 15.1.1.2)

Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline per Modification 3 (Section 15.1.1.3)

Old text:

The study comprises a screening phase (Visit 1; ~~-8 weeks [± 10 days]~~ to Day 1), Baseline (Visit 2, Day 1), a 72-week treatment phase for the 2Q8 group~~, and up to 76 weeks for the extended dosing group~~. All post-baseline study visits may deviate by ± 3 days.

New text:

The study comprises a screening phase (Visit 1; up to 66 days prior to Day 1), Baseline (Visit 2, Day 1), a 72-week treatment phase (for the 2Q8 group), and a final study visit at Week 76 or an early termination visit. All scheduled post-baseline study visits may deviate by ± 3 days relative to baseline.

Section 9.1 Tabular schedule of evaluations

Clarification of the period durations per Modification 2 (Section 15.1.1.2)

Time windows were consolidated for all post-baseline visits in both treatment groups to ± 3 days relative to baseline per Modification 3 (Section 15.1.1.3)

Clarification that the final visit procedures should also be conducted in the case of early termination per Modification 16 (Section 15.1.1.16)

Addition of urine dipstick test at the baseline visit per Modification 17 (Section 15.1.1.17)

Added foot note (numbered now as h) 'The urine dipstick pregnancy test is to be repeated as frequently as required following the investigator's medical judgment and local regulations' to the Tabular schedule of evaluations; added that it is required at Visit 13 (final visit or early termination); and moved the pregnancy test in the Schedule of assessments and study procedures from Initiation procedures to Standard safety per Modification 18 (Section 15.1.1.18).

Arranging the footnotes in the order the table is read, line by line; and minor clarifications regarding pre-and post-dose assessments for indirect ophthalmoscopy and IOP per Modification 19 (Section 15.1.1.19)

Removed sample study drug injection protocol from the appendix per Modification 20 (Section 15.1.1.20).

Old text:

Table 9-1: Schedule of assessments and study procedures

Visit number [a]	*Screening* Visit 1	*Baseline (BL)* Visit 2	Visits 3 - 8	*Prim. compl.* Visit 9	Visits 10 - 12	*Final visit* Visit 13[h]
Time point[a] 2Q8 group / Extended-dosing group	~~-8 weeks~~ to BL (~~±10 days~~) (both groups)	Day 1 (both groups)	Weeks 8 – 48 / Flex. intervals (≥8 weeks)	Week 52 (both groups)	Week 56, 64, 72 / Flex. intervals (≥8 weeks)	Week 76 (both groups)
Initiation procedures						
Informed consent	●					
Demographic data	●					
Medical / ophthalmic history	●					
Physical examination	●					
~~Serum pregnancy test (women of childbearing potential only)~~	~~●~~					
PT / INR and PTT	●					
Inclusion / exclusion criteria	●	●				
Study medication						
Randomization		●				
Administration of study treatment [f]		●	●	extended-dosing only [i]	●	extended-dosing only [i,j]
Ophthalmologic assessments						
BCVA (ETDRS chart starting at 4 m) [g]	●	●	●	●	●	●
Optical coherence tomography	●	●	●	●	●	●
~~Fluorescein angiogr., fundus photogr.~~	~~●~~			●		●
Indirect ophthalmoscopy [d]	●	●	●	●	●	●
Slit lamp biomicroscopy	●	●	●	●	●	●
Intraocular pressure (IOP) [e]	●	●	●	●	●	●
Standard safety						
Prior / concomitant medications	●	●	●	●	●	●
Adverse events [c]		●	●	●	●	●
Vital signs (temp., blood pressure, HR)	●	●	●	●	●	●
Hematology / chemistry	●					●
Urinalysis / UPCR	●					●
Other						
NEI VFQ-25 [b]		●		●		●

BCVA = Best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; HR = heart rate;
NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; PT/INR = Prothrombin time / International normalized ratio; PTT = Partial thromboplastin time; UPCR = Urine protein/creatinine ratio

a: ~~Visit schedules~~ may deviate by ± 3 days relative to baseline. Scheduled visits should not be altered due to the deviation of the previous visit.
Visit numbers refer to the mandatory visits for treatment administration to subjects in the 2Q8 group. Fewer visits may be required for subjects in the extended-dosing group, for whom extended-dosing intervals are indicated.
b: The NEI VFQ-25 is to be administered in a quiet room by a person certified to administer the questionnaire
c: Any AE occurring up to 4 weeks after the last injection of aflibercept has to be documented, regardless of the relationship to the study drug or the seriousness of the event and reported in accordance with this protocol (i.e. not as a spontaneous report). For any drug-related AE occurring after 4 weeks after the last application of aflibercept, the standard procedures that are in place for spontaneous reporting will be followed.
d: ~~Pre- and~~ post-~~dose~~ at visits with study drug administration
e: ~~Pre-dose and~~ 30-60 minutes post-injection at visits with study drug administration
~~f: See Section 16.1 for an example study drug injection protocol.~~
g: Refraction to be done at each visit
~~h: Also to be conducted in case of premature discontinuation of study participation~~
i: Extended-dosing subjects may receive injections at Week 52 or 76 depending on their individual schedule.
j: If an extended-dosing subject receives an injection at Week 76, follow-up is needed on any adverse events (including ongoing events) that may occur within 4 weeks following this treatment (AE reporting under this protocol; i.e. not as spontaneous reports)

New text:

Table 9-1: Schedule of assessments and study procedures

Visit number [a]	*Screening* Visit 1	*Baseline (BL)* Visit 2	Visits 3 - 8	*Prim. compl.* Visit 9	Visits 10 - 12	*Final visit* Visit 13 *or early term.*
Time point[a] 2Q8 group / Extended-dosing group	Up to 66 days prior to BL (both groups)	Day 1 (both groups)	Weeks 8 – 48 / Flex. intervals (≥8 weeks)	Week 52 (both groups)	Week 56, 64, 72 / Flex. intervals (≥8 weeks)	Week 76 (both groups)
Initiation procedures						
Informed consent	●					
Demographic data	●					
Medical / ophthalmic history	●					
Physical examination	●					
PT / INR and PTT	●					
Inclusion / exclusion criteria	●	●				
Study medication						
Randomization		●				
Administration of study treatment		●	●	extended-dosing only [b]	●	extended-dosing only [b,c]
Ophthalmologic assessments						
BCVA (ETDRS chart starting at 4 m) [d]	●	●	●	●	●	●
Optical coherence tomography	●	●	●	●	●	●
FA, FP	●			●		●
Indirect ophthalmoscopy [e]	●	●	●	●	●	●
Slit lamp biomicroscopy	●	●	●	●	●	●
Intraocular pressure (IOP) [f]	●	●	●	●	●	●

a: All post-baseline visits may deviate by ± 3 days relative to baseline. In the 2Q8 group, scheduled visits should not be altered due to the deviation of the previous visit.
Visit numbers refer to the mandatory visits for treatment administration to subjects in the 2Q8 group. Fewer visits may be required for subjects in the extended-dosing group, for whom extended-dosing intervals are indicated.

b: Extended-dosing subjects may receive injections at Week 52 or 76 depending on their individual schedule.

c: If an extended-dosing subject receives an injection at Week 76, follow-up is needed on any adverse events (including ongoing events) that may occur within 4 weeks following this treatment (AE reporting under this protocol; i.e. not as spontaneous reports)

d: Refraction to be done at each visit

e: Also post-injection at visits with study drug administration

f: Also 30-60 minutes post-injection at visits with study drug administration

(Table continued on next page)

Table 9-1 (continued): Schedule of assessments and study procedures

Visit number [a]	*Screening* **Visit 1**	*Baseline (BL)* **Visit 2**	**Visits 3 - 8**	*Prim. compl.* **Visit 9**	**Visits 10 - 12**	*Final visit* **Visit 13** *or early term.*
Time point[a] 2Q8 group / **Extended-dosing group**	**Up to 66 days prior to BL** (both groups)	**Day 1** (both groups)	**Weeks 8 – 48** / **Flex. intervals** (≥8 weeks)	**Week 52** (both groups)	**Week 56, 64, 72** / Flex. intervals (≥8 weeks)	**Week 76** (both groups)
Standard safety						
Prior / concomitant medications	●	●	●	●	●	●
Adverse events [g]		●	●	●	●	●
Vital signs (temp., blood pressure, HR)	●	●	●	●	●	●
Hematology / chemistry	●					●
Urinalysis / UPCR	●					●
Serum pregnancy test (women of childbearing potential only)	●					
Urine dipstick pregnancy test (women of childbearing potential only) [h]		●				●
Other						
NEI VFQ-25 [i]		●		●		●

BCVA = Best corrected visual acuity; early term. = early termination; ETDRS = Early Treatment Diabetic Retinopathy Study; FA = fluorescein angiography; FP = fundus photography; HR = heart rate; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; PT/INR = Prothrombin time / International normalized ratio; PTT = Partial thromboplastin time; UPCR = Urine protein/creatinine ratio

a: All post-baseline visits may deviate by ± 3 days relative to baseline. In the 2Q8 group, scheduled visits should not be altered due to the deviation of the previous visit.
Visit numbers refer to the mandatory visits for treatment administration to subjects in the 2Q8 group. Fewer visits may be required for subjects in the extended-dosing group, for whom extended-dosing intervals are indicated.

g: Any AE occurring up to 4 weeks after the last injection of aflibercept has to be documented, regardless of the relationship to the study drug or the seriousness of the event and reported in accordance with this protocol (i.e. not as a spontaneous report). For any drug-related AE occurring after 4 weeks after the last application of aflibercept, the standard procedures that are in place for spontaneous reporting will be followed.

h: The urine dipstick pregnancy test is to be repeated as frequently as required following the investigator's medical judgment and local regulations.

i: The NEI VFQ-25 is to be administered in a quiet room by a person certified to administer the questionnaire

Section 9.2.1 Screening visit (Visit 1)

Clarification of the period durations per Modification 2 (Section 15.1.1.2); replaced reference of study manual with reference to reading center acquisition protocol per Modification 7 (Section 15.1.1.7)

Old text:

Scheduling: Both treatment groups: ~~Week -8 (± 10 days)~~ to Day 1

…

- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Fundus photography (FP) and fluorescein angiography (FA) [86]
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intra-ocular pressure (IOP)

New text:

Scheduling: Both treatment groups: Up to 66 days prior to Day 1

…

- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Fundus photography (FP) and fluorescein angiography (FA) [87]
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intra-ocular pressure (IOP)

86 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~~.

87 The reading center acquisition protocol will further specify the standards for FA/FP during the study.

Section 9.2.2 Baseline visit (Visit 2)

Added a urine dipstick pregnancy test to the baseline visit per Modification 17 (Section 15.1.1.17)

Clarified the re-assessment of inclusion and exclusion criteria at the Baseline visit per Modification 21 (Section 15.1.1.21)

Post-injection ocular assessments added per Modification 22 (Section 15.1.1.22)

Old text:

Scheduling: Both treatment groups: Day 1

The following procedures will be performed at this visit:

- ~~Assessment~~ of inclusion and exclusion criteria (see Sections 6.1 and 6.2 for details)
- Randomization (see Section 7.3 for details)
- …
- Application of study medication (see Section 7.4 for details)

New text:

Scheduling: Both treatment groups: Day 1

The following procedures will be performed at this visit:

- Re-check of inclusion and exclusion criteria (see Sections 6.1 and 6.2 for details)
  - Including urine dip stick pregnancy test for women of childbearing potential
- Randomization (see Section 7.3 for details)
- …
- Application of study medication (see Section 7.4 for details)
- Post-injection ocular assessments (see Section 9.4.1 for details):
  - Indirect ophthalmoscopy
  - Intraocular pressure (IOP)

Section 9.2.3 Visits between baseline and Week 52

Post-injection ocular assessments added per Modification 22 (Section 15.1.1.22)

Old text:

…

- Application of study medication (see Section 7.4 for details)

New text:

…

- Application of study medication (see Section 7.4 for details)
- Post-injection ocular assessments (see Section 9.4.1 for details):
  - Indirect ophthalmoscopy
  - Intraocular pressure (IOP)

Section 9.2.4 Primary completion (Week 52)

Replaced reference of study manual with reference to reading center acquisition protocol per Modification 7 (Section 15.1.1.7)

Post-injection ocular assessments for subjects in the extended dosing group who receive study medication at this visit added per Modification 22 (Section 15.1.1.22)

Old text:

The following procedures will be performed at this visit:

- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Fundus photography (FP) and fluorescein angiography (FA) [88]
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
- Record of concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Vital signs (body temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Record of NEI VFQ-25 (see Section 9.7 for details)

88 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~~.

New text:

The following procedures will be performed at this visit:

- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Fundus photography (FP) and fluorescein angiography (FA) [89]
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
- Record of concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Vital signs (body temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Record of NEI VFQ-25 (see Section 9.7 for details)

Subjects in the extended dosing group if they receive injections at this visit (depending on their individual schedule):

- Application of study medication (see Section 7.4 for details)
- Post-injection ocular assessments (see Section 9.4.1 for details):
  - Indirect ophthalmoscopy
  - Intraocular pressure (IOP)

89 The reading center acquisition protocol will further specify the standards for FA/FP during the study.

Section 9.2.5 Visits between primary completion (Week 52) and end of study (Week 76)

Changed end of study visit to final visit per Modification 16 (Section 15.1.1.16)

Added the full list of study procedures instead of a reference only per Modification 23 (Section 15.1.1.23)

Post-injection ocular assessments added per Modification 22 (Section 15.1.1.22)

Old text:

Section 9.2.5 Visits between primary completion (Week 52) and ~~end of study~~ visit (Week 76)

Scheduling:

- 2Q8 group: Fixed visit schedule every 8 weeks **Visits 10 (Week 56) to 12 (Week 72)**
- Extended-dosing group: Individualized flexible schedule with intervals ≥8 weeks **Visit numbers depend on individual schedule** (extended-dosing subjects may have fewer visits than 2Q8 subjects)

~~The conduct of any of these visits will be identical to the visits between baseline and Week 52 as described in Section 9.2.3.~~

New text:

Section 9.2.5 Visits between primary completion (Week 52) and final visit (Week 76)

Scheduling:

- 2Q8 group: Fixed visit schedule every 8 weeks **Visits 10 (Week 56) to 12 (Week 72)**
- Extended-dosing group: Individualized flexible schedule with intervals ≥8 weeks **Visit numbers depend on individual schedule** (extended-dosing subjects may have fewer visits than 2Q8 subjects)

The following procedures will be performed at any of these visits:

- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intra-ocular pressure (IOP)

- Record of concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Vital signs (body temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Application of study medication (see Section 7.4 for details)
- Post-injection ocular assessments (see Section 9.4.1 for details):
  - Indirect ophthalmoscopy
  - Intraocular pressure (IOP)

Section 9.2.6 End of study (Week 76)

Clarified that the final visit procedures should also be conducted in the case of early termination per Modification 16 (Section 15.1.1.16)

Added that a urine dipstick pregnancy test is required at the final visit or early termination per Modification 18 (Section 15.1.1.18)

Post-injection ocular assessments for subjects in the extended dosing group who receive study medication at this visit added per Modification 22 (Section 15.1.1.22)

Added the full list of study procedures instead of a reference only per Modification 23 (Section 15.1.1.23)

Old text:

Section 9.2.6 ~~End of study~~ (Week 76)

Scheduling: Both treatment groups: Week 76

~~The conduct of any of this visit will be identical to the visit at Week 52 as described in Section 9.2.4.~~

New text:

Section 9.2.6 Final visit (Week 76) or early termination

Scheduling: Both treatment groups: Week 76

This visit will also be conducted in case of early termination of a subject.

The following procedures will be performed at this visit:

- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Fundus photography (FP) and fluorescein angiography (FA) [90]
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intra-ocular pressure (IOP)
- Record of concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Vital signs (body temperature, blood pressure and heart rate) (see Section 9.6.3.3 for details)
- Urine dip stick pregnancy test for women of childbearing potential
- Record of NEI VFQ-25 (see Section 9.7 for details)

Subjects in the extended dosing group if they receive injections at this visit (depending on their individual schedule):

- Application of study medication (see Section 7.4 for details)
- Post-injection ocular assessments (see Section 9.4.1 for details):
  - Indirect ophthalmoscopy
  - Intraocular pressure (IOP)

90 The reading center acquisition protocol will further specify the standards for FA/FP during the study.

Section 9.4.1.1 Best corrected visual acuity

Removed reference to study manual and added references to reading center acquisition protocol for FA and FP per Modification 7 (Section 15.1.1.7)

Old text:

Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985) at starting at 4 meters. Visual Acuity (VA) examiners must be certified to ensure consistent measurement of BCVA. ~~A detailed protocol for conducting VA 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 (The Early Treatment Diabetic Retinopathy Study Group, 1985) at starting at 4 meters. Visual Acuity (VA) examiners must be certified to ensure consistent measurement of BCVA.

Section 9.4.1.2 Optical coherence tomography (OCT)

Reworded description of OCT in efficacy section per Modification 24 (Section 15.1.1.24).

Old text:

Retinal and lesion characteristics will be evaluated using OCT ~~on the study eye. For all visits where the OCT procedure is scheduled, images on the study eye and fellow eye will be captured, transmitted to, and read by the independent reading center; at screening, OCT images will be captured on both eyes.~~ All OCTs will be electronically archived at the study sites as part of the source documentation. OCT technicians must be certified by the reading center to ensure consistency and quality in image acquisition.

New text:

Retinal and lesion characteristics will be evaluated using OCT. OCT-images of the study eye and fellow eye will be captured, transmitted to, and read by the independent reading center. All OCTs will be electronically archived at the study sites as part of the source documentation. OCT technicians and equipment must be certified by the reading center to ensure consistency and quality in image acquisition.

Section 9.4.1.6 Fundus photography (FP) and fluorescein angiography (FA)

Replaced reference of study manual with reference to reading center acquisition protocol per Modification 7 (Section 15.1.1.7)

Added requirement to archive FA and FP images electronically, clarified the confirmation of eligibility by the reading center, and re-ordered paragraphs per Modification 25 (Section 15.1.1.25)

Old text:

The anatomical state of the retinal vasculature of the study eye will be evaluated by funduscopic examination, FP and FA.

The study eye will be the transit eye. For all visits where the funduscopic examination, FP, and FA procedure are scheduled, FP and FA will be performed on both eyes. ~~FP and FA from the screening visit (Visit 1) will be captured and transmitted for both eyes and reviewed before randomization.~~

Fundus and angiographic images will be sent to an independent reading center where images will be read. All FA and FP images will be archived at the site as part of the source documentation. Although FA is performed on both eyes, only the study eye will be evaluated by the independent reading center. Photographers must be certified by the reading center to ensure consistency and quality in image acquisition.

A detailed protocol for FP and FA image acquisition and assessment can be found in the ~~FA Study Manual~~ [91].

The treating investigator may perform additional FA/FP at other times during the study based on his/her medical judgment and standard of care.

New text:

The anatomical state of the retinal vasculature of the study eye will be evaluated by funduscopic examination, FP and FA.

The study eye will be the transit eye. For all visits where the funduscopic examination, FP, and FA procedure are scheduled, FP and FA will be performed on both eyes.

Fundus and angiographic images will be sent to an independent reading center where images will be read. All FA and FP images will be archived electronically at the site as part of the source documentation. Although FA is performed on both eyes, only the study eye will be evaluated by the independent reading center. Photographers must be certified by the reading center to ensure consistency and quality in image acquisition.

91 ~~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~~.

FP and FA from the screening visit (Visit 1) will be captured and transmitted for both eyes to an independent reading center where images will be read. A formal check will be done and eligibility will be confirmed by the reading center before randomization.

A detailed protocol for FP and FA image acquisition and assessment can be found in the reading center acquisition protocol[92].

The treating investigator may perform additional FA/FP at other times during the study based on his/her medical judgment and standard of care.

Section 9.6.1.1 Definitions

Removal of reference to ECG per Modification 26 (Section 15.1.1.26)

Old text:

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

New text:

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.

Section 9.6.1.2.4 Action taken with study treatment

Removal of "Dose reduced" from possible actions taken with study treatment per Modification 27 (Section 15.1.1.27)

Old text:

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

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

92 The reading center acquisition protocol will further specify the standards for FA/FP during the study.

New text:

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

Section 9.6.1.5 Expected adverse events

Reference to summary of product characteristics replaced with reference to local label for information on AEs per Modification 28 (Section 15.1.1.28).

Old text:

~~For this study, the applicable reference document is the most current version of the summary of product characteristics.~~

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

New text:

Information on AEs with an onset after the first application of the test drug is provided in the local label.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

Section 9.6.2 Pregnancies

New paragraph on fertility and guidance regarding the follow-up after birth added to the pregnancy section per Modification 29 (Section 15.1.1.29)

Old text:

The investigator must report to the sponsor any pregnancy occurring in a female study subject during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

For 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.

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

New text:

The investigator must report to the sponsor any pregnancy occurring in a female study subject during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

The child's health should be followed up until three months after birth.

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.

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

Results from animal studies with high systemic exposure indicate that aflibercept can impair male and female fertility. Such effects are not expected after ocular administration with very low systemic exposure.

Section 9.6.3.1 Laboratory evaluations

Specification and timing of pregnancy test changed per Modification 17 (Section 15.1.1.17) and Modification 18 (Section 15.1.1.18)

Clarification of time point of blood withdrawal with respect to FA per Modification 30 (Section 15.1.1.30)

Old text:

Laboratory evaluation will be conducted according to the schedule provided in Section 9.1.

Blood will be drawn by direct venipuncture.

Safety laboratory parameters to be evaluated are summarized in Table 9-2.

The exact date and time (24-hour clock) of each blood sample obtained will be recorded on the appropriate eCRF page. All laboratory tests will be performed at a central laboratory. A copy of the results will be filed in the source documentation.

Table 9-2: Laboratory safety parameters

Chemistry	**Urinalysis**	**Hematology**
Sodium	Glucose	Hemoglobin
Potassium	Protein	Hematocrit
Chloride	Specific Gravity	Red blood cell count
Calcium	Blood	Mean corpuscular volume (MCV)
Glucose	Ketones	Mean corpuscular hemoglobin concentration (MCHC)
Albumin	Protein:Creatinine Ratio (UPCR)	Mean corpuscular hemoglobin (MCH)
Total Protein, Serum		Leucocyte count
Creatinine		Differential count
Blood urea nitrogen (BUN)	**Coagulation**	Neutrophils
Aspartate aminotransferase (AST)	Prothrombin time (PT)	Lymphocytes
Alanine aminotransferase (ALT)	Partial thromboplastin time (PTT)	Monocytes
Alkaline phosphatase	International normalized ratio (INR)	Basophils
Total bilirubin		Eosinophils
Amylase		Platelet count
Total cholesterol		
HDL cholesterol		
~~Serum~~ pregnancy test for women of childbearing potential		

HDL: high-density lipoprotein

New text:

Laboratory evaluation will be conducted according to the schedule provided in Section 9.1 (beyond that schedule, pregnancy tests are to be done in women of childbearing potential as frequently as outlined in Table 9-1).

Blood will be drawn before FA by direct venipuncture.

Safety laboratory parameters to be evaluated are summarized in Table 9-2.

The exact date and time (24-hour clock) of each blood sample obtained will be recorded on the appropriate eCRF page. All laboratory tests will be performed at a central laboratory. A copy of the results will be filed in the source documentation.

Table 9-2: Laboratory safety parameters - amended

Chemistry	**Urinalysis**	**Hematology**
Sodium	Glucose	Hemoglobin
Potassium	Protein	Hematocrit
Chloride	Specific Gravity	Red blood cell count
Calcium	Blood	Mean corpuscular volume (MCV)
Glucose	Ketones	Mean corpuscular hemoglobin concentration (MCHC)
Albumin	Protein:Creatinine Ratio (UPCR)	Mean corpuscular hemoglobin (MCH)
Total Protein, Serum		Leucocyte count
Creatinine		Differential count
Blood urea nitrogen (BUN)	**Coagulation**	Neutrophils
Aspartate aminotransferase (AST)	Prothrombin time (PT)	Lymphocytes
Alanine aminotransferase (ALT)	Partial thromboplastin time (PTT)	Monocytes
Alkaline phosphatase	International normalized ratio (INR)	Basophils
Total bilirubin		Eosinophils
Amylase		Platelet count
Total cholesterol		
HDL cholesterol		
Pregnancy test for women of childbearing potential (see Table 9-1)		

HDL: high-density lipoprotein

Section 9.7 Patient-reported outcome -NEI VFQ-25

Requirement to document the name of the person assisting the subject in completing the NEI VFQ-25 questionnaire added per Modification 31 (Section 15.1.1.31)

Old text:

Vision-related quality of life will be assessed using the NEI VFQ-25 questionnaire (Section 16.1). This questionnaire will be presented in the local language and should be administered in a quiet room by a person certified to administer this type of questionnaire, preferably before other visit procedures are performed. For subjects unable to read the questionnaire owing to vision impairment, a family member, other legal representative of the subject, study nurse, or study physician may assist the subject in completing the questionnaire.

New text:

Vision-related quality of life will be assessed using the NEI VFQ-25 questionnaire (Section 16.1). This questionnaire will be presented in the local language and should be administered in a quiet room by a person certified to administer this type of questionnaire, preferably before other visit procedures are performed. For subjects unable to read the questionnaire owing to vision impairment, a family member, other legal representative of the subject, study nurse, or study physician may assist the subject in completing the questionnaire. In this case, the name of that person should be documented.

Section 10.3.2.2 Efficacy analyses

Added example of possible analysis per Modification 35 (Section 15.1.1.35)

Old text:

As sensitivity analyses, the primary efficacy and key secondary efficacy analyses will be repeated on the Per-Protocol Set as defined in Section 10.2.

New text:

As sensitivity analyses, the primary efficacy and key secondary efficacy analyses will be repeated on the Per-Protocol Set as defined in Section 10.2.

The analysis can also include, if applicable, BCVA evolution over the course of pre-study aflibercept treatment, starting with the initial BCVA value as captured in the first set of inclusion criteria. Snellen-equivalents may therefore be converted into ETDRS letter scores.

Section 11.3 Data processing

Removal of reference to ECG per Modification 26 (Section 15.1.1.26)

Minor rewording (changed examples) per Modification 32 (Section 15.1.1.32)

Old text:

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 CRF as well as for data from other sources (e.g. IVRS, laboratory, ~~ECG, ePRO,~~ adjudication committees).

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

New text:

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 CRF as well as for data from other sources (e.g. IVRS, laboratory, reading center, adjudication committees).

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

Section 13.4 Subject information and informed consent

Revised to align with sponsor standards per Modification 33 (Section 15.1.1.33).

Old text:

Each subject will be informed about the following aspects of premature withdrawal:

…

- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. 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.~~

…

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

New text:

Each subject will be informed about the following aspects of premature withdrawal:

…

- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The subject has the right to object to the generation and processing of this post-withdrawal data.

…

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

<u>If the subject is unable to read the informed consent form due to vision impairment, a family member, other legal representative of the subject, study nurse, or study physician should read the document verbatim to the subject. A discussion and explanation, including answering all questions from the subject, should also occur prior to the subject or their legal representative signing the form. An impartial witness should be present during the entire informed consent discussion. The witness must be unaffiliated with the conduct of the study, and will also sign and date the document along with the subject or their legal representative.</u>

Section 16.1 Drug administration protocol

Removal of the Appendix Drug administration protocol per Modification 20 (Section 15.1.1.20).

~~**Section 16.1 Drug administration protocol**~~

~~Study Drug Dose and Volume for Administration.~~

~~The supplied kits include a fill needle, injection needle and 1 syringe.~~

~~VEGF Trap-Eye is formulated as a sterile liquid to a final concentration of 40 mg/mL VEGF Trap in 5% sucrose, 10 mM sodium phosphate pH 6.3, 0.03% polysorbate 20, and 40 mM NaCl in water for injection. VEGF Trap-Eye study drug will be supplied by the sponsor in sealed, sterile 2-mL vials each with a withdrawable volume of 0.5 mL. The volume of injection will be 50 µL (0.05 mL) for the 2 mg dose of VEGF Trap. The study drug will be withdrawn using aseptic technique through an 18 gauge fill 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.~~

~~VEGF Trap-Eye vials are to be stored at 2°C to 8°C. Freezing of the drug is to be avoided. 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. Exposure of the material to temperatures outside these limits, except for warming prior to administration, is not recommended and may result in loss of activity. Records of actual storage conditions (i.e. temperature log) at the study site must be maintained; and must include a record of the dates, when the refrigerator was checked, the initials of person checking, and the temperature.~~

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

16. Appendices

16.1 National Eye Institute 25-item visual function questionnaire

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

Per Amendment 2 (Section 15.1.1.20,) the Drug administration protocol was removed from the appendix.

Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is*:

(Circle One)

READ CATEGORIES:

Excellent	1
Very Good	2
Good	3
Fair	4
Poor	5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

READ CATEGORIES:

Excellent	1
Good	2
Fair	3
Poor	4
Very Poor	5
Completely Blind	6

* Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0

3. How much of the time do you worry about your eyesight?

(Circle One)

READ CATEGORIES:

None of the time 1
A little of the time 2
Some of the time 3
Most of the time 4
All of the time? 5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

READ CATEGORIES:

None 1
Mild 2
Moderate 3
Severe, or 4
Very severe? 5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4
Stopped doing this because of your eyesight 5
Stopped doing this for other reasons or not interested in doing this 6

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

8. How much difficulty do you have reading street signs or the names of stores?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Stopped doing this because of your eyesight	5
Stopped doing this for other reasons or not interested in doing this	6

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes..... 1 ***Skip To Q 15c***

No 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove ..... 1 ***Skip To Part 3, Q 17***

Gave up 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ..... 1 ***Skip To Part 3, Q 17***

Mainly other reasons ..... 2 ***Skip To Part 3, Q 17***

Both eyesight and other reasons..... 3 ***Skip To Part 3, Q 17***

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all 1
A little difficulty..... 2
Moderate difficulty..... 3
Extreme difficulty 4

16. How much difficulty do you have driving at night? Would you say you have: **(READ CATEGORIES AS NEEDED)**

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

16a. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have: **(READ CATEGORIES AS NEEDED)**

	(Circle One)
No difficulty at all	1
A little difficulty	2
Moderate difficulty	3
Extreme difficulty	4
Have you stopped doing this because of your eyesight	5
Have you stopped doing this for other reasons or are you not interested in doing this	6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	(Circle One On Each Line)				
17. Do you accomplish less than you would like because of your vision?.	1	2	3	4	5
18. Are you limited in how long you can work or do other activities because of your vision?	1	2	3	4	5
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

		Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20.	I stay home most of the time because of my eyesight.	1	2	3	4	5
21.	I feel frustrated a lot of the time because of my eyesight.....	1	2	3	4	5
22.	I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23.	Because of my eyesight, I have to rely too much on what other people tell me.	1	2	3	4	5
24.	I need a lot of help from others because of my eyesight.....	1	2	3	4	5
25.	I worry about doing things that will embarrass myself or others, because of my eyesight.....	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.