Document Type:	Study Protocol
Official Title:	An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of three different treatment regimens of 2 mg aflibercept administered by intravitreal injections to subjects with diabetic macular edema (DME)
NCT Number:	NCT02818998
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1. Title page

An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of three different treatment regimens of 2 mg aflibercept administered by intravitreal injections to subjects with diabetic macular edema (DME)

Efficacy and safety of three different aflibercept regimens in subjects with DME

Test drug:	BAY 86-5321; aflibercept; Eylea		
Study purpose:	Posology comparison		
Clinical study phase:	3b	Date:	07 December 2015
Registration:	EudraCT: 2014-004938-25	Version no.:	1.0
Sponsor's study no.:	BAY 86-5321 / 17613		
Sponsor:	**Bayer HealthCare AG, D-51368 Leverkusen, Germany**		

Sponsor's medical expert: PPD
Email: PPD
Phone: 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: 8-12-2015 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

Title	An open-label, randomized, active-controlled, parallel-group, Phase-3b study of the efficacy, safety, and tolerability of three different treatment regimens of 2 mg aflibercept administered by intravitreal injections to subjects with diabetic macular edema (DME)
Short title	Efficacy and safety of three different aflibercept regimens in subjects with DME
Clinical study phase	3b
Study objective(s)	Primary objective To evaluate the efficacy of long-term treatment with 2 mg aflibercept via different intravitreal (IVT) treatment regimens to subjects with DME pre-treated with 2 mg aflibercept every 8 weeks after 5 initial monthly injections for approximately 1 year or more (according to the EU label for the first year of treatment) Secondary objective To assess the safety and tolerability of different treatment regimens of aflibercept in this population
Test drug(s)	
Name of active ingredient	BAY 86-5321 / aflibercept / Eylea
Dose(s)	For each parallel treatment group 2 mg aflibercept per injection Posology: 2Q8fix Fixed injection intervals: 8 weeks (reference arm). No monitoring visits between treatment visits. Treatment cessation Usually, treatment should not be ceased in this reference arm. However, temporary treatment cessation can be considered if the investigator has reason to believe that at the respective time point treatment is not in the patient's best interest. The patient should return for evaluation as the investigator considers appropriate depending on the patient's condition. Treatment re-start Treatment should be restarted once the condition leading to cessation of treatment is resolved. In case of recurrence of DME it is proposed to begin with the same regimen as a de novo treatment, i.e. five monthly injections followed by a 2Q8 regimen. 2Q8ext Flexible dosing regimen per EU label, injection interval ≥ 8 weeks. No monitoring visits between treatment visits. Treatment cessation Cessation of treatment can be considered if the interval between two injections reaches or exceeds 16 weeks and if this duration can be maintained for at least two consecutive intervals without need for shortening of the interval, i.e. with stable visual and anatomic outcome parameters. If treatment is halted, the patient should return for monitoring visits at least every 16 weeks. Treatment re-start Treatment should be restarted if a deterioration of visual and anatomic outcome parameters occurs. If treatment has to be restarted due to recurrence of DME, it is proposed to begin with the same regimen as a de novo treatment, i.e. five monthly injections followed by a 2Q8 regimen.

	2PRN Monthly monitoring with dosing as needed Treatment cessation If there is no recurrence of active disease, treatment is terminated until such time, if ever, that the disease recurs. The monthly monitoring is continued throughout. Treatment re-start Treatment will be resumed with single injections each time the re-treatment criteria are met.
Route of administration	Intravitreal (IVT) injection
Duration of treatment	2 years
Reference drug(s)	none
Indication	Diabetic macular edema (DME)
Diagnosis and main criteria for inclusion /exclusion	• Adults of either sex, ≥ 18 years of age • The subject's history of aflibercept treatment meets all of the following: a. Treatment in the study eye was initiated with five monthly (-1 week / +2 weeks) doses of 2 mg aflibercept and improvements of visual and anatomic outcomes were observed and documented. 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 8 weeks (±10 days) before the first planned treatment / randomization in this study. e. Total prior treatment duration with aflibercept (i.e. from first aflibercept treatment ever to enrollment into this study) was 1 year or longer. To be met at initiation of pre-study aflibercept treatment: • Type-1 or -2 diabetes mellitus • Diagnosis of DME secondary to diabetes mellitus involving the center of the macula (defined as the area of the center subfield of OCT) in the study eye • Decrease in vision determined to be primarily the result of DME in the study eye • BCVA in the study eye of ETDRS letter score 73 to 24 (corresponding to a Snellen equivalent of approximately 20/40 to 20/320)
Study design	Randomized, 3-arm, active-controlled, parallel-group, open-label, multicenter
Methodology	Visual function of the study eye and the fellow eye will be assessed using the ETDRS protocol starting at 4 meters. Refraction is to be done at each visit.
Type of control	Active control
Data Monitoring Committee	An adjudication committee will perform an additional analysis of arterial thrombotic events (ATEs)
Number of subjects	Total of approximately 490 subjects should be randomized (163 per treatment group)
Primary variable(s)	Change in ETDRS BCVA letter score for the study eye from baseline to Week 52
Time point/frame of measurement for primary variable(s)	After 52 weeks of randomized treatment

Plan for statistical analysis	The primary analysis of the primary efficacy variable will be conducted on the full analysis set (FAS). The analyses are repeated on the PPS. Statistical testing will be conducted to prove the non-inferiority of each of the two extended-dosing regimens to the 2Q8 fixed-dosing regimen. To control the overall type-I error rate for multiple comparisons, Hochberg procedure (Hochberg 1988) will be used to adjust for multiplicity. The hypotheses for the two extended dosing regimen will be based on an analysis of covariance (ANCOVA) model with the baseline measure as a covariate and treatment group and "10-letter gain from start of aflibercept treatment to baseline (yes/no)" as a fixed factor.

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List of abbreviations

2PRN	2 mg aflibercept pro re nata (as needed)
2Q8	2 mg aflibercept administered every 8 weeks
2Q8ext	2 mg aflibercept at injection intervals ≥ 8 weeks
2Q8fix	2 mg aflibercept at injection intervals of exactly 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 Classification System
ATE	arterial thrombotic event
BCVA	best corrected visual acuity
BUN	blood urea nitrogen
CNV	choroidal neovascularization
CRF	case record form
CRO	contract research organization
CRT	central retinal thickness
CSR	clinical study report
CTFG	Clinical Trials Facilitation Group
DME	diabetic macular edema
DR	diabetic retinopathy
DRSS	diabetic retinopathy severity scale
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
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HbA1c	glycohemoglobin A1c
HDL	high density lipoprotein
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IOP	intraocular pressure
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVT	intravitreal(ly)
IxRS	interactive (x) response system
LOCF	last observation carried forward
MAH	marketing authorization holder
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire 25
OCT	optical coherence tomography
PDR	proliferative diabetic retinopathy
PID	subject identification number
PPS	per-protocol set
PRN	Latin: *pro re nata* (as needed)
PT/INR	prothrombin time
PTT	partial thromboplastin time
QoL	quality of life
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SAS	statistical analysis software
SD-OCT	spectral domain optical coherence tomography
SMT	safety management team
SOC	system organ class
SUSARs	suspected, unexpected, serious adverse reaction
UPCR	urine protein/creatinine ratio
VA	visual acuity
VEGF	vascular endothelial growth factor
WHO-DD	World Health Organization Drug Dictionary

3. Introduction

3.1 Background

Diabetic retinopathy is a major cause of visual impairment. Diabetic macular edema (DME) is a manifestation of DR and is the most frequent cause of blindness in young and mid-aged adults (Moss et al. 1998). It is estimated that 4.8% of the global population has diabetic retinopathy, while 3% to 4.1% of Europeans are affected (Prokofyeva & Zrenner 2012).

Vascular endothelial growth factor (VEGF), a protein growth factor that both stimulates angiogenesis and increases vascular permeability, plays a key role in the pathophysiology of DME (Bhagat et al. 2009). Hypoxia and other metabolic factors trigger VEGF release. VEGF induces vascular leakage and neovascularization. While neovascularization is the most severe manifestation of DR, vascular leakage leading to macular edema is an important cause of reduced visual acuity (VA).

VEGF Trap-Eye is a recombinantly produced fusion protein consisting of the Fc domain of human IgG1 fused to portions of the human VEGF receptor extracellular domains. It has a high binding affinity for VEGF and can neutralize VEGF mediated biological activity. Therefore, VEGF Trap-Eye may effectively block a key pathway in DME pathophysiology.

The approval of aflibercept in the EU (August 2014) was based upon the results of two randomized, multicenter, double-masked, active-controlled Phase-3 clinical studies, VISTA DME and VIVID DME. The primary endpoint of these studies was the change from baseline to Week 52 in BCVA in ETDRS letter score. Both studies demonstrated that aflibercept, dosed every 8 weeks following five initial monthly injections, provided efficacy that was superior to laser treatment, the former standard of care.

The approved EU label for aflibercept states:

> *The recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres.*
>
> *Eylea treatment is initiated with one injection per month for five 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. The schedule for monitoring should be determined by the treating physician.*
>
> *If visual and anatomic outcomes indicate that the subject is not benefiting from continued treatment, Eylea should be discontinued.*

3.2 Rationale of the study

The approved dosing schedule for the first year of DME treatment has been thoroughly studied during the clinical development program and is well supported by the available data as originally submitted.

For additional support of the approved dosing schedule for the second year of treatment and beyond, the MAH seeks to collect further data including information on treatment cessation and restart. To this end, the present study is initiated. It is designed to meet requests made by EMA as part of a post-approval commitment.

3.3 Benefit-risk assessment

Throughout the entire study, all subjects enrolled will receive active treatment approved for DME with close medical supervision according to established local standard of care.

Taken together, participation in this study is not expected to bear an undue risk for the enrolled subjects.

4. Study objectives

Primary objective

To evaluate the efficacy of long-term treatment with 2 mg aflibercept via different intravitreal (IVT) treatment regimens to subjects with DME pre-treated with 2 mg aflibercept every 8 weeks after 5 initial monthly injections for approximately 1 year or more (according to the EU label for the first year of treatment)

Secondary objective

To assess the safety and tolerability of different treatment regimens of aflibercept in this population

5. Study design

Design overview

This is a randomized, 3-arm, active-controlled, parallel-group, open-label, multicenter, Phase-3b study to be conducted in subjects pre-treated with aflibercept for 1 year or more. Aflibercept 2 mg administered at a fixed schedule every 8 weeks (2Q8fix) is regarded as the reference arm. Two alternative regimens will be compared to the reference arm: A regimen with a gradually extended dosing interval according to the current EU label (2Q8ext) and a *pro re nata* dosing scheme (2PRN) with monthly monitoring (Figure 1).

Figure 1: Overall study design

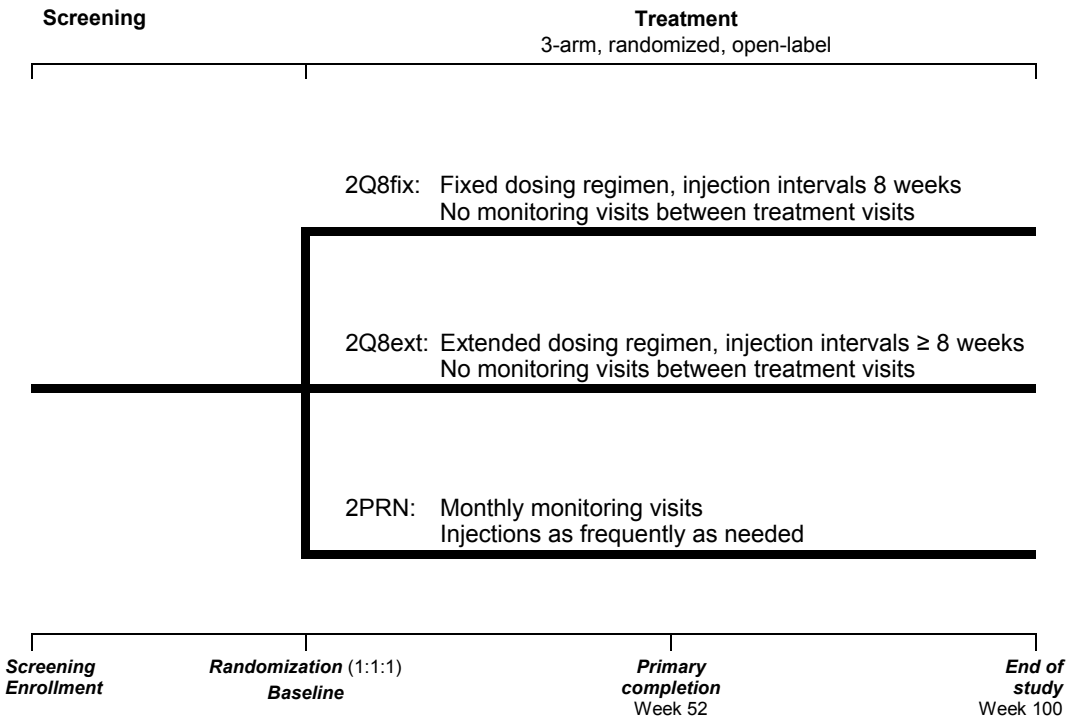

Table 1 shows the detailed treatment schedules and procedures for temporary cessation of treatment.

Table 1: Treatment administration and cessation

Detailed administration schedule	Treatment cessation and re-start
2Q8fix Fixed injection intervals: 8 weeks throughout the entire treatment period After the baseline visit, the subjects return every 8 weeks to the investigational site. Starting at the baseline visit, they receive an injection at each visit. The last injection will be at Week 96. The final safety and efficacy assessments are done at Week 100 (final visit). There will be no pure monitoring visits, i.e. without treatment (with the exception of Week 52 [primary completion] and Week 100 [final visit]).	**Treatment cessation** Usually, treatment should not be ceased in this reference arm. However, temporary treatment cessation can be considered if the investigator has reason to believe that at the respective time point treatment is not in the patient's best interest. The patient should return for evaluation as the investigator considers appropriate depending on the patient's condition. **Treatment re-start** Treatment should be restarted once the condition leading to cessation of treatment is resolved. In case of recurrence of DME it is proposed to begin with the same regimen as a de novo treatment, i.e. five monthly injections followed by a 2Q8 regimen.
2Q8ext Flexible injection intervals: ≥ 8 weeks (no upper limit) At the baseline visit and at each subsequent visit, the investigator will determine the duration until the subject's next injection, based on visual and anatomic outcomes at the current visit. Injection intervals can be extended if visual and anatomic measures are stable. When/if edema recurs, the treatment interval should be reverted to the last treatment interval when the disease was inactive. The increments and decrements for the injection intervals are at the investigator's discretion; typically, increments of 2 weeks are recommended. There will be no pure monitoring visits, i.e. an injection will be given at each visit with the (potential) exception of Weeks 52 and 100. At Weeks 52 and 100, an injection can be given if this visit coincides with a scheduled injection visit. All subjects return for efficacy and safety assessments at Week 52 (primary endpoint assessment). The final safety and efficacy assessments will be done at Week 100 (final visit).*	**Treatment cessation** Cessation of treatment can be considered if the interval between two injections reaches or exceeds 16 weeks and if this duration can be maintained for at least two consecutive intervals without need for shortening of the interval, i.e. with stable visual and anatomic outcome parameters. If treatment is halted, the patient should return for monitoring visits at least every 16 weeks. **Treatment re-start** Treatment should be restarted if a deterioration of visual and anatomic outcome parameters occurs. If treatment has to be restarted due to recurrence of DME, it is proposed to begin with the same regimen as a de novo treatment, i.e. five monthly injections followed by a 2Q8 regimen.
2PRN After randomization, the subjects return every 4 weeks to the investigational site. At each visit, the investigator will determine, based on pre-specified re-treatment criteria, whether an injection is to be given or not. Injection decision will be based on the investigator's judgment using the following re-treatment criteria: • Leakage as sign of active DME (e.g. CRT as assessed by SD-OCT > 300 µm and/or an increase of > 50 µm from best previous measurement) • Increase of ≥ 5 letters in BCVA between current and most recent previous visit • Loss of ≥ 5 letters from the previous BCVA measurement with any increase in SD-OCT CRT The last visit with an option for treatment under this protocol is at Week 96. The final safety and efficacy assessments will be done at Week 100 (final visit).	**Treatment cessation** If there is no recurrence of active disease, treatment is terminated until such time, if ever, that the disease recurs. The monthly monitoring is continued throughout. **Treatment re-start** Treatment will be resumed with single injections each time the re-treatment criteria are met.

For all treatment groups, the time window for all visits is ± 3 days relative to baseline.
BCVA: best corrected visual acuity
CRT: central retinal thickness
PRN: Latin: pro re nata (as needed)
SD OCT: spectral domain optical coherence tomography

*If an extended-dosing subject receives an injection at Week 100, 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).

Randomization will be stratified by 10-letter gain from start of aflibercept treatment ("yes"/"no" as obtained from available medical documentation). For each group, the first injection of study medication will be given at the baseline visit.

Owing to the nature of the different dosing regimens, the three arms will not have the same visit and treatment schedule. Therefore, masking of the treatments is not feasible.

For each treatment group, the assessment of the primary endpoint will be performed at Week 52.

For each treatment group, the time window for all visits is ± 3 days relative to baseline. After the final visit or after early termination, all subjects return to standard-of-care treatment outside of this study.

Efficacy and safety assessments will be performed throughout the study as detailed in the schedule of evaluations in Section 9.

Primary variable

The primary efficacy variable is the change in best corrected visual acuity (BCVA; as measured by the ETDRS letter score) from baseline (i.e. randomization) to Week 52.

Justification of the design

Open-label setting: Since all treatment groups will be on different visit schedules, masking the study is impossible. Masking the study would require harmonizing the visit schedules in all groups by having subjects in the 2Q8 groups 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.

The primary endpoint will be assessed at the end of the first year of treatment under this protocol. As the protocol is designed, subjects completing one year in the study will have also completed the end of their second year of treatment given that subjects entering this study will have received a first year of treatment outside of this study. The results of the primary endpoint at week 52 of this study (after at least two years of treatment with aflibercept) will be reported in a stand-alone clinical study report to make this important information available to the community as soon as possible.

End of study

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

6. Study population

Selection of the study eye

Only one eye will be designated as the study eye.

6.1 Inclusion criteria

A subject must meet all of the following inclusion criteria as applicable to be eligible for enrollment into this study:

To be met at screening and baseline for this study

1. Adults of either sex, ≥ 18 years of age
2. The subject's history of aflibercept treatment meets all of the following:
   a. Treatment in the study eye was initiated with five monthly (-1 week / +2 weeks) doses of 2 mg aflibercept and improvements of visual and anatomic outcomes were observed and documented.
   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 8 weeks (±10 days) before the first planned treatment / randomization in this study.
   e. Total prior treatment duration with aflibercept (i.e. from first aflibercept treatment ever to enrollment into this study) was 1 year or longer.

   Adherence to Criterion 2 will be checked on the basis of the available medical documentation. If no information is available, this inclusion criterion is considered as not fulfilled and the subject cannot be included in the study.
3. Willingness and ability to comply with clinic visits and study-related procedures
4. Women and men of reproductive potential must agree to a method of highly effective contraception (as defined by the Clinical Trials 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 (IUD)
- Intrauterine hormone-releasing system (IUS)
- 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 Clinical Trials Facilitation group [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.

5. Negative pregnancy test (serum test at screening; urine dip stick test at baseline; women of childbearing potential only)
6. Signed written informed consent

<u>To be met at initiation of pre-study aflibercept treatment</u>

The check of adherence to these criteria will be based on available medical documentation. If no information is available, the respective inclusion criterion is considered as not fulfilled and the subject cannot be included in the study.

7. Type-1 or -2 diabetes mellitus
8. Diagnosis of DME secondary to diabetes mellitus involving the center of the macula (defined as the area of the center subfield on OCT) in the study eye
9. Decrease in vision determined to be primarily the result of DME in the study eye
10. BCVA in the study eye of ETDRS letter score 73 to 24
    This corresponds to a Snellen equivalent of approximately 20/40 to 20/320.

6.2 Exclusion criteria

A subject must not meet any of the following exclusion criteria as applicable to be eligible for enrollment into this study. The check of these criteria at initiation of pre-study aflibercept treatment (referred to as "first aflibercept injection") will be based on available medical documentation. If no information is available, the exclusion criterion is considered fulfilled and the subject cannot be included in the study.

At initiation of pre-study aflibercept treatment

1. Previous treatment with anti-angiogenic drugs in study eye (e.g. pegaptanib sodium, bevacizumab, ranibizumab or aflibercept) within the last 12 weeks before initiation of aflibercept pre-study treatment

At *all* of the following time points

- Initiation of pre-study aflibercept treatment
- Screening for this study
- Baseline for this study

2. History of vitreoretinal surgery and/or including scleral buckling in the study eye
3. Prior treatment of the study eye with
   - Long acting steroids, either periocular or intraocular, in the preceding 120 days or
   - Iluvien® intravitreal implant at any time
4. Active proliferative diabetic retinopathy (PDR), current iris neovascularization, vitreous hemorrhage, or tractional retinal detachment in the study eye
5. Aphakia in the study eye
6. Cataract surgery within 90 days before aflibercept treatment in the study eye
7. Yttrium-aluminum-garnet capsulotomy in the study eye within 30 days before aflibercept treatment
8. Any other intraocular surgery within 90 days of aflibercept treatment in the study eye
9. Ocular inflammation (including trace or above) or history of uveitis in the study eye
10. Vitreomacular traction or epiretinal membrane in the study eye evident biomicroscopically or on OCT that was thought to affect central vision
11. Pre-retinal fibrosis involving the macula of the study eye
12. Structural damage to the center of the macula in the study eye that was likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia or organized hard exudates

13. Concurrent disease in the study eye, other than DME, that could compromise VA, require medical or surgical intervention during the study period, or could confound interpretation of the results (including advanced glaucoma, retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization of any cause)
14. Myopia of a spherical equivalent prior to any possible refractive or cataract surgery of ≥ 8 diopters in the study eye
15. Administration of systemic anti angiogenic agents within 180 days before aflibercept treatment
16. Uncontrolled diabetes mellitus as defined by hemoglobin (Hb)A1c > 12.0%
17. Uncontrolled blood pressure (defined as systolic blood pressure > 160 mmHg or diastolic blood pressure > 95 mmHg while subject is sitting confirmed in two separate measurements)
18. Presence of any contraindications indicated in the EU commission/locally approved label for aflibercept

At *all* of the following time points

- Screening for this study
- Baseline for this study.

19. Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye
20. Any ocular or periocular infection in the preceding 4 weeks in either eye
21. Filtration surgery for glaucoma in the past or likely to be needed in the future on the study eye
22. Uncontrolled glaucoma (defined as intraocular pressure [IOP] > 25 mmHg despite treatment with antiglaucoma medication) in the study eye
23. Allergy or hypersensitivity to fluorescein
24. Current treatment for a serious systemic infection
25. History of either cerebral vascular accident and/or myocardial infarction within 180 days before aflibercept treatment
26. Renal failure requiring dialysis or renal transplant
27. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, might affect interpretation of the results of the study, or renders the subject at high risk for treatment complications
28. Significant media opacities, including cataract, in the study eye that interferes with visual acuity, fundus photography or OCT imaging.
29. Breast-feeding women
30. Previous receipt of at least 1 dose of study drug under this protocol

31. Concomitant participation in another clinical study with investigational medicinal product(s). Exception: A temporal overlap with participation in Bayer study protocol 17850 is acceptable.
32. 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

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 current aflibercept therapy needs to be replaced by another treatment for DME.
- AE (ocular or non-ocular) that, from the subject's or the investigator's view, is potent enough to require withdrawal from the study. 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".

In general, re-starting the defined set of screening procedures to enable the "screening failure" subject's participation at a later time point is not allowed. Thus, in general, participation of an initial "screening failure" subject at a later time point is not acceptable even if he/she meets all selection criteria upon re-screening.

However, as an exception, re-screening may be acceptable under the following conditions:

- The subject had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- The in- / exclusion criteria preventing the subject's initial attempt to participate have been changed (via protocol amendment).
- The reason for the screening failure was subsequently resolved (e.g. decrease of elevated IOP, controlled arterial hypertension) within 30 days.

Under any of the above exceptions, a subject may be re-screened once only. To be eligible, re-screened subjects must meet all selection criteria at the re-screening visit.

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

Dropout

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

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 (Premature termination of the study).

6.3.2 Replacement

Subjects who withdraw from the study will not be replaced.

6.4 Subject identification

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

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.

7. Treatments

7.1 Treatments to be administered

As detailed in the inclusion criterion 2 (Section 6.1), all subjects to be randomized into this study are required to have received at least 1 year of treatment with aflibercept.

Each eligible subject will be randomized (1:1:1) to one of three parallel treatment groups specified in Table 2.

Table 2: Treatment groups

	2Q8fix	2Q8ext	2PRN
Dose per injection	Aflibercept 2 mg	Aflibercept 2 mg	Aflibercept 2 mg
Regimen	Fixed dosing regimen, injection interval: 8 weeks (reference arm). No monitoring visits between treatment visits.	Flexible dosing regimen per EU label, injection interval: ≥ 8 weeks. No monitoring visits between treatment visits.	Monthly monitoring with dosing as needed.
Last study treatment	Week 96	Week 100 or earlier [b]	Week 96 or earlier
Final safety and efficacy assessments	Week 100	Week 100 [c]	Week 100
Planned number of randomized subjects	163	163	163
Detailed administration schedule [a]	See Section 5, Table 1		
Treatment cessation	See Section 5, Table 1		

BCVA: best corrected visual acuity; CRT: central retinal thickness; PRN: Latin: *pro re nata* (as needed); SD-OCT: spectral domain optical coherence tomography

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

b At Week 100, subjects receive an injection if this visit coincides with a scheduled injection visit.

c. If an extended-dosing subject receives an injection at Week 100, 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).

7.2 Identity of study treatment

The identity of the study drug is summarized in Table 3.

Table 3: 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 – 10 mM sodium phosphate – 0.03% polysorbate 20 – 40 mM 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 three dosing regimens. The three treatment groups will be randomly assigned by the central randomization group in a 1:1:1 ratio to one of the three parallel treatment arms identified in Section 7.1. Treatment assignment will be controlled via the IxRS.

Randomization will be stratified by 10-letter gain from start of aflibercept treatment ("yes"/"no" as obtained from available medical documentation).

7.4 Dosage and administration

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 Section 7.2, Table 3 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.

Posology

Treatment posology is detailed in Table 4. Re-treatment criteria for the 2PRN arm are specified in Section 7.1, Table 2.

Table 4: Treatment posology

	2Q8fix		2Q8ext		2PRN	
	Visit	**Treatment**	**Visit**	**Treatment**	**Visit**	**Treatment**
Screening	mandatory Visit 1	no treatment	mandatory Visit 1	no treatment	mandatory Visit 1	no treatment
Baseline	**mandatory Visit 2**	**mandatory**	**mandatory Visit 2**	**mandatory**	**mandatory Visit 2**	**mandatory**
Week 4	no visit		no visit		mandatory Visit 3	*throughout all visits between Week 4 and Week 96, treatment is optional according to the re-treatment criteria given in Section 7.1, Table 2*
Week 8	mandatory visit with treatment		*between Week 8 and Week 52, visits (incl. treatment) can be scheduled at any time point (provided injection intervals are ≥ 8 weeks)*		mandatory Visit 4	
Week 12	no visit				mandatory Visit 5	
Week 16	mandatory visit with treatment				mandatory Visit 6	
Week 20	no visit				mandatory Visit 7	
Week 24	mandatory visit with treatment				mandatory Visit 8	
Week 28	no visit				mandatory Visit 9	
Week 32	mandatory visit with treatment				mandatory Visit 10	
Week 36	no visit				mandatory Visit 11	
Week 40	mandatory visit with treatment				mandatory Visit 12	
Week 44	no visit				mandatory Visit 13	
Week 48	mandatory visit with treatment				mandatory Visit 14	
Week 52	**mandatory**	**no treatment**	**mandatory**	**optional**	**mandatory Visit 15**	
Week 56	mandatory visit with treatment		*between Week 52 and Week 100, visits (incl. treatment) can be scheduled at any time point (provided injection intervals are ≥ 8 weeks)*		mandatory Visit 16	
Week 60	no visit				mandatory Visit 17	
Week 64	mandatory visit with treatment				mandatory Visit 18	
Week 68	no visit				mandatory Visit 19	
Week 72	mandatory visit with treatment				mandatory Visit 20	
Week 76	no visit				mandatory Visit 21	
Week 80	mandatory visit with treatment				mandatory Visit 22	
Week 84	no visit				mandatory Visit 23	
Week 88	mandatory visit with treatment				mandatory Visit 24	
Week 92	no visit				mandatory Visit 25	
Week 96	mandatory visit with treatment				mandatory Visit 26	
Week 100	**mandatory**	**no treatment**	**mandatory**	**optional**	**mandatory Visit 27**	**no treatment**

The reasons for treatment cessation – and if applicable re-start – will be documented. The treatment schedule in the 2Q8fix and 2Q8ext groups may deviate from the schedule proposed in Section 7.4, Table 4 if cessation and re-start become necessary (see Section 5, Table 1). However, the visits at week 52 and 100 since baseline are mandatory for all subjects regardless of any temporary cessation of treatment.

Consideration of special warnings based on 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 best-corrected visual acuity (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*

7.5 Masking

Not applicable - this is an open-label study.

7.6 Drug logistics and accountability

Packaging

Aflibercept will be supplied by the sponsor in treatment kits described in Section 7.4.

Supply

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

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 or blister pack 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.

Accountability

On the day of receipt, the responsible site personnel will confirm receipt of study drug via IxRS. 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.

8. Non-study therapy

8.1 Prior and concomitant 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.

8.1.1 Prior therapy

In particular, any potential previous treatments for DME 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

Subjects may not receive any standard or investigational pharmacological agents for treatment of their DME in the study eye other than aflibercept as specified in this protocol until they have completed the assessments scheduled for the Completion / Early Termination visit. This includes medications administered locally (e.g. IVT, by juxtascleral or periorbital routes), as well as those administered systemically with the intent of treating either eye. Ocular laser photocoagulation or surgery may be performed if deemed necessary by the investigator.

8.1.2.2 Fellow-eye treatment

If the fellow eye shall be treated pharmacologically, the most applicable 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 the fellow (non-study) eye has DME, the fellow eye may receive any locally approved non-systemic treatment (note that fellow-eye aflibercept treatment may be used under this protocol).

Even if treated with aflibercept, the fellow eye will not be considered an additional study eye.

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 standard of care.

8.2 Post-study therapy

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

9. Procedures and variables

9.1 Tabular schedule of evaluations

Table 5: Schedule of assessments and procedures

	Screening [b]	*Baseline* [b]		*Primary completion*		*Final visit / early termination*
Visit number [a]	**Visit 1**	**Visit 2**	**Visits 3 - 14**	**Visit 15**	**Visits 16 - 26**	**Visit 27**
Timing *2PRN* [c]	**individualized** for all treatment groups	**Day 1** for all treatment groups	**Week 4 - 48**	**Week 52** for all treatment groups	**Week 56 - 96**	**Week 100** for all treatment groups
Timing *2Q8fix* [c]			**Week 8 - 48**			
Timing *2Q8ext* [c]			**individualized**		**individualized**	
Initiation procedures						
Informed consent	●					
Demographic data	●					
Medical / ophthalmic history	●					
Check of in-/exclusion criteria	●	●				
Randomization		●				
Study medication						
Administration of study treatment		●	○[d]	○[d]	○[d]	○[d]
Ophthalmologic assessments (all assessments bilaterally [additional assessments may occur outside of this protocol])						
BCVA (ETDRS chart starting at 4 m) [e]	●	●	●	●	●	●
Optical coherence tomography	●		mand./option.[f]	●	mand./option.[f]	●
Fluorescein angiogr., fundus photogr.	●		optional [g]	●	optional [g]	●
Indirect ophthalmoscopy	●	●	●	●	●	●
Slit lamp biomicroscopy	●	●	●	●	●	●
Intraocular pressure (IOP)	●	●	●	●	●	●
Patient-reported outcomes						
NEI VFQ-25		●		●		●
Standard safety						
Prior / concomitant medications	●	●	●	●	●	●
Adverse events [h]	●	●	●	●	●	●
Hematology / chemistry	●			●		●
Urinalysis / UPCR	●			●		●
Pregnancy test [i] Serum	●					
Pregnancy test [i] Urine		●	○[i]	●	○[i]	●
Vital signs (temp., blood pressure, pulse)	●			●		●

BCVA = best corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; PT/INR = prothrombin time / international normalized ratio; PTT = partial thromboplastin time; UPCR = urine protein / creatinine ratio

a. Visit numbers refer to the mandatory visits for treatment administration to subjects in the 2PRN group. Fewer visits are required for subjects in the 2Q8fix or 2Q8ext groups.

b. If all data needed for enrollment are available, the screening visit and the baseline visit may take place on the same day. In such a case, procedures scheduled for both visits will be conducted only once.
Scheduling of screening and baseline visit(s) has to ensure that the first injection of study medication under this protocol meets the respective criteria for the pre-study treatment as specified in Section 6.1, inclusion criterion 2.d.

c. Scheduling of the post-baseline visits (except Week 52 and Week 100): 2PRN, fixed schedule every 4 weeks; 2Q8fix: fixed schedule every 8 weeks; 2Q8ext: individualized. Visits at Week 52 and Week 100 are mandatory for all treatment groups.
Visit schedules may deviate by ± 3 days relative to baseline.

d. Treatment schedules differ across treatment groups; details are provided in Section 7.4, Table 4.

e. Refraction to be done at each visit

f. Mandatory for 2PRN subjects. Otherwise to be done only if deemed necessary by the investigator or required by local medical practice.

g. To be done only if deemed necessary by the investigator or required by local medical practice.

h. Any AE occurring up to 4 weeks after the last injection of aflibercept has to be documented, regardless of the causal 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. All potential arterial thrombotic events (ATEs) will be adjudicated according to the Antiplatelet Trialists' Collaboration (APTC).
If a 2Q8ext subject receives an injection at Week 100, follow-up is needed on any AEs (including ongoing events) that may occur within 4 weeks following this treatment (AE reporting under this protocol; i.e. not as spontaneous reports)

i. In women of childbearing potential only. The test is to be repeated as frequently as requested.

9.2 Visit description

9.2.1 Screening

Scheduling (identical for all subjects of all treatment groups)

If all data needed for enrollment are available, the screening visit and the baseline visit may take place on the same day. In such a case, procedures scheduled for both visits will be conducted only once.

Scheduling of screening and baseline visit(s) has to ensure that the first injection of study medication under this protocol meets the respective criteria for the pre-study treatment as specified in inclusion criterion 2.d (Section 6.1).

Conduct

The following procedures will be performed at this visit:

- Obtaining signed informed consent form (see Section 13.4 for details).
- Record of demographic data (see Section 9.3.1 for details)
- Record of prior and concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Record of medical and ophthalmic history (see Section 9.3.2 for details)
- Assessment of inclusion and exclusion criteria (see Sections 6.1 and 10 for details)
  (If screening and baseline visits take place on different days, the assessable selection criteria are to be met on both days.)
- Laboratory assessments (see Section 9.6.3.1 for details):
  - Hematology panel
  - Chemistry panel
  - 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
- Pregnancy test in women of childbearing potential (serum test)
- Vital signs (body temperature, blood pressure and pulse) (see Section 9.6.3.2 for details)

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

9.2.2 Baseline

Scheduling (identical for all subjects of all treatment groups)

If all data needed for enrollment are available, the screening visit and the baseline visit may take place on the same day. In such a case, procedures scheduled for both visits will be conducted only once.

Scheduling of screening and baseline visit(s) has to ensure that the first injection of study medication under this protocol meets the respective criteria for the pre-study treatment as specified in inclusion criterion 2.d (Section 6.1).

Conduct

The following procedures will be performed at this visit:

- Assessment of inclusion and exclusion criteria (see Sections 6.1 and 10 for details)
  (If screening and baseline visits take place on different days, all selection criteria are to be met on both days.)
- Randomization (see Section 7.3 for details)
- Record of prior and concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- NEI VFQ-25 (see Section 9.4.3 for details)
- Pregnancy test in women of childbearing potential (urine dip stick test)
- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart starting at 4 m (refraction is to be done at each visit)
  - Indirect ophthalmoscopy (also post injection)
  - Slit lamp biomicroscopy
  - Intraocular pressure (IOP) (also post injection)
  - First application of study medication (see Section 7.4 for details).

Injections are to take place *after* completion of the procedures listed above.

9.2.3 Visits after baseline and before Week 52

Scheduling

The scheduling of visits after baseline and before Week 52 differs among treatment groups (see Section 5):

– 2Q8fix Fixed schedule for each subject in this treatment group:
Visits take place in strict accordance with the Q8 schedule, i.e. at Weeks 8, 16, 24 etc.

– 2Q8ext Individualized visit schedule. Visit interval ≥ 8 weeks

– 2PRN Fixed schedule for each subject in this treatment group:
Visits every 4 weeks

The treatment schedule in the 2Q8fix and 2Q8ext groups may deviate from the schedule proposed in Section 7.4, Table 4 if cessation and re-start become necessary (see Section 5, Table 1). If a subject returns for a monitoring visit during temporary treatment cessation, the procedures described for a visit in the PRN treatment group should be performed. If treatment is re-started, the paradigms described in Section 5, Table 1 should be followed in accordance with the subject's assigned treatment group.

Conduct

The following procedures will be performed:

- Record of prior and concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart starting at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT) - mandatory for PRN, otherwise optional
  - Optional: Fundus photography (FP) and fluorescein angiography (FA)
  - Indirect ophthalmoscopy (also post injection if applicable)
  - Slit lamp biomicroscopy
  - Intraocular pressure (IOP) (also post injection if applicable)
- Application of study medication (see Section 7.4 for details) as follows:
  - 2Q8fix: Treatment at each visit
  - 2Q8ext: Treatment at each visit
  - 2PRN: Treatment only if re-treatment criteria (see Section 7.1, Table 2) are met
  - Record reason for cessation/restart of treatment if applicable

  Injections are to take place *after* completion of the procedures listed above.

9.2.4 Week 52

Scheduling (identical for all subjects of all treatment groups)

All subjects of all treatment groups will have this visit; it will be scheduled for Week 52 (± 3 days) after baseline.

Conduct

The following procedures will be performed:

- Record of prior and concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- NEI VFQ-25 (see Section 9.4.3 for details)
- Laboratory assessments (see Section 9.6.3.1 for details):
  - Hematology panel
  - Chemistry panel
  - 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
- Pregnancy test in women of childbearing potential (urine dip stick test)
- Vital signs (body temperature, blood pressure and pulse) (see Section 9.6.3.2 for details)
- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart starting at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Fundus photography (FP) and fluorescein angiography (FA)
  - Indirect ophthalmoscopy (also post injection if applicable)
  - Slit lamp biomicroscopy
  - Intraocular pressure (IOP) (also post injection if applicable)
- Application of study medication (see Section 7.4 for details) as follows:
  - 2Q8fix: No treatment
  - 2Q8ext: Treatment only if according to individualized treatment schedule
  - 2PRN: Treatment only if re-treatment criteria (see Section 7.1, Table 2) are met.

Injections are to take place *after* completion of the procedures listed above.

9.2.5 Visits after Week 52 and before Week 100

Scheduling and conduct of the visits after Week 52 and before Week 100 will follow the specifications for visits after baseline and before Week 52 as described in Section 9.2.3.

9.2.6 Week 100 (final visit or early termination)

Scheduling (identical for all subjects of all treatment groups)

All subjects of all treatment groups will have this visit; it will be scheduled for Week 100 (± 3 days) after baseline.

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

Conduct

The following procedures will be performed:

- Record of prior and concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- NEI VFQ-25 (see Section 9.4.3 for details)
- Laboratory assessments (see Section 9.6.3.1 for details):
  - Hematology panel
  - Chemistry panel
  - 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
- Pregnancy test in women of childbearing potential (urine dip stick test)
- Vital signs (body temperature, blood pressure and pulse) (see Section 9.6.3.2 for details)
- Ocular assessments (see Section 9.4.1 for details):
  - BCVA using ETDRS chart starting at 4 m (refraction is to be done at each visit)
  - Optical coherence tomography (OCT)
  - Fundus photography (FP) and fluorescein angiography (FA)
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intraocular pressure (IOP).
- Application of study medication (see Section 7.4 for details) as follows:
  - 2Q8ext: Treatment only if according to individualized treatment schedule
    If treated at this visit, subjects are to be followed up for AEs as specified in Section 9.1, Table 5 Footnote h.

  The other treatment groups do not receive study drug at this visit.

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:

- Start before signing of the informed consent
- Considered relevant for the subject's study eligibility.

In particular, the following will be asked for:

- Duration of diabetes
- Type of diabetes (Type 1/2)
- Diabetic retinopathy (including first diagnosis, intensity)
- First diagnosis of DME
- Smoking history

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 selection criteria as defined in Section 6. To this end, the subjects must provide informed consent to allow review of medical records from the time of first aflibercept treatment.

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 5. Ophthalmic examinations will be conducted on both eyes. At any visit, ophthalmic examinations not stipulated by this protocol may take place outside of this protocol at the discretion of the investigator.

If applicable, all ophthalmic evaluations are to be performed before study drug injection.

9.4.1.1 Best corrected visual acuity

Visual function will be assessed using the ETDRS protocol (Early Treatment Diabetic Retinopathy Study Research Group 1985) starting at 4 meters. Refraction is to be done at each visit. Visual Acuity (VA) examiners must be certified to ensure consistent measurement of BCVA.

9.4.1.2 Optical coherence tomography (OCT)

Retinal and lesion characteristics will be evaluated using SD-OCT. For all visits where the OCT procedure is scheduled, images will be captured and read by the investigator.

All OCTs will be archived electronically at the study sites as part of the source documentation. All protocol-mandated OCTs will be sent to the central reading center for evaluation and storage.

9.4.1.3 Indirect ophthalmoscopy

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

9.4.1.4 Slit lamp biomicroscopy

The slit lamp examination will be performed according to local medical practice and applicable medical standards at the site.

9.4.1.5 Intraocular pressure (IOP)

IOP is to be measured using applanation tonometry (Goldmann, Tonopen or other approved alternatives). The same method of IOP measurement must be used in each subject throughout the study.

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)

The anatomical state of the retinal vasculature of the study eye will be evaluated by funduscopic examination, FP and FA. Fundus and angiographic images will be read by the investigator for the individual treatment decisions. All FA and FP images will be archived electronically at the site as part of the source documentation. All protocol-mandated FA and FP images will be sent to the central reading center for evaluation and storage.

The 7-Field-FP for both eyes will be transmitted to the central reading center for ETDRS diabetic retinopathy severity scale (DRSS) grading and storage.

9.4.2 Efficacy variables

All efficacy variables derived from the ophthalmic examinations are specified in Section 10.3.2.2.

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

Vision-related QoL will be assessed using the NEI VFQ-25 questionnaire (see Section 16.1 for details).

This questionnaire will be presented in the local language and should be administered in a quiet room by a study-related person qualified to administer this type of questionnaire, preferably before other visit procedures are performed. For subjects unable to read the questionnaire due to vision impairment, a family member, other legal representative of the subject, study nurse, or study physician may assist the subject in completing the questionnaires. In this case, the name of that person should be documented.

9.5 Pharmacokinetics / pharmacodynamics

not applicable

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

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 patient 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).

Medical history versus adverse event

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.

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

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 the injection procedure.

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

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

– Drug withdrawn

– Drug interrupted

– Dose not changed

– Not applicable

– Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

– None

– Remedial drug therapy

– Other

9.6.1.2.6 Outcome

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

– Recovered/resolved

– Recovering/resolving

– Recovered/resolved with sequelae

– Not recovered/not resolved

– Fatal

– Unknown

9.6.1.3 Assessments and documentation of adverse events

Attention is to be paid to the occurrence of 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 AE
- The date of onset
- The maximum intensity
- Any study drug action and other action taken by the investigator to resolve the AE
- Any specific drug or non-drug treatment of the AE

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

ATE analysis

Potential arterial thrombotic events (ATEs) will be evaluated by a masked adjudication committee according to criteria formerly applied and published by the Anti-Platelet Trialists' Collaboration (APTC) (Antithrombotic Trialists' Collaboration 2002). The definition of ATEs as well as further details are described in the adjudication committee charter.

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

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.

9.6.2 Pregnancies

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.

9.6.3 Further safety

9.6.3.1 Laboratory evaluations

Laboratory evaluations 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 requested).

Blood will be drawn by direct venipuncture.

Safety laboratory parameters to be evaluated are summarized in Table 6.

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

Table 6: 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)
HbA1c	Protein:Creatinine Ratio (UPCR)	Mean corpuscular hemoglobin (MCH)
Albumin		Leucocyte count
Total Protein, Serum	Pregnancy test for women of childbearing potential (either urine or serum test as specified and Section 9.1 and 9.2)	Differential count
Creatinine		Neutrophils
Blood urea nitrogen (BUN)		Lymphocytes
Aspartate aminotransferase (AST)		Monocytes
Alanine aminotransferase (ALT)		Basophils
Alkaline phosphatase		Eosinophils
Total bilirubin		Platelet count
Amylase		
Total cholesterol		
HDL cholesterol		

HDL: High density lipoprotein

According to current 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 laboratory.

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

9.6.3.2 Vital signs (temperature, blood pressure and pulse)

Vital signs include body temperature, blood pressure (diastolic and systolic), and pulse. They will be taken according to the schedule provided in Section 9.1. Measurements should be done in a consistent and standardized way according to locally established practice.

9.7 Other procedures and variables

Not applicable

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.

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

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 until Week 52. 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 time points (primary, secondary, exploratory) are specified in Table 7.

Table 7: Efficacy variables

Variable	Ranking	
	Week 52	Week 100
Change from baseline in ETDRS BCVA letter score for the study eye	Primary	Secondary
Change from baseline in CRT in the study eye	Secondary	Secondary
Proportion of subjects who gained ≥ 10, ≥ 15 letters	Secondary	Secondary
Proportion of subjects who lost ≥ 30 letters	Secondary	Secondary
Total number of intravitreal injections required in the study eye	Exploratory	Exploratory
Total number of visits	Exploratory	Exploratory
Proportion of subjects who lost ≥ 0, ≥ 5, ≥ 10, ≥ 15 letters	Exploratory	Exploratory
Proportion of subjects who gained ≥ 0, ≥ 5 letters	Exploratory	Exploratory
Total number of OCT / FA / FP procedures	Exploratory	Exploratory
Mean change from baseline in NEI VFQ-25 total score	Exploratory	Exploratory

BCVA: best corrected visual acuity; CNV: choroidal neovascularization; CRT: central retinal thickness; ETDRS: Early Treatment Diabetic Retinopathy Study

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

10.3.1.2 Safety variables

The following safety variables will be assessed:

- Adverse events
- Vital signs
- Ophthalmological safety variables (see 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 (WHO-DD).

The number of injections will be tabulated in all 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

10.3.2.2.1 Primary efficacy variable

The primary efficacy variable is the (absolute) change from baseline in ETDRS BCVA letter score for the study eye to Week 52.

The primary analysis of the primary efficacy variable will be conducted on the full analysis set (FAS). The analyses will be repeated on the PPS to provide supportive evidence (sensitivity analysis).

Statistical testing will be conducted to prove the non-inferiority of each of the two extended-dosing regimens to the 2Q8 fixed-dosing regimen. The corresponding hypotheses are

1. **P_{2Q8ext}:** Null hypothesis $H_{01}: \mu_{2Q8ext} \leq \mu_{2Q8fix}-D$ versus
   Alternative hypothesis $H_1: \mu_{2Q8ext} > \mu_{2Q8fix} -D$,
2. **P_{2PRN}:** Null hypothesis $H_{01}: \mu_{2PRN} \leq \mu_{2Q8fix} -D$ versus
   Alternative hypothesis $H_1: \mu_{2PRN} > \mu_{2Q8fix} -D$,

where

D = non-inferiority margin chosen as 4 letters (see below for a justification)

μ_{2Q8ext} = true mean change in BCVA letter score for the study eye from baseline to Week 52 in the 2Q8ext treatment regimen

μ_{2Q8fix} = true mean change in BCVA letter score for the study eye from baseline to Week 52 in the 2Q8fix dosing treatment regimen

μ_{2PRN} = true mean change in BCVA letter score for the study eye from baseline to Week 52 in the 2PRN treatment regimen

To control the overall type-I error rate for multiple comparisons, Hochberg procedure (Hochberg 1988) as implemented in PROC Multtest in SAS will be used to adjust for multiplicity. The two hypotheses stated above will be tested based on an analysis of covariance (ANCOVA) model with the baseline measure as a covariate and treatment group and "10-letter gain from start of aflibercept treatment to baseline (yes/no)" as a fixed factor:

The observation of subject *i* receiving treatment *t* can be written as follows:

$$Y_{itr} = \mu_t + \gamma_j + x_i\beta + \varepsilon_{it}$$

with

μ_t denoting the treatment effect for treatment *t* (2Q8ext, 2Q8fix, 2PRN),

γ_j denoting the effect of the stratification variable "10-letter gain from start of aflibercept treatment (yes/no)"

x_i denoting the baseline BCVA of subject *i,*

β denoting the coefficient associated with baseline BCVA and

$\varepsilon_{it} \sim N(0, \sigma_t^2)$ denoting the residual error.

Justification of the non-inferiority margin

Previous studies with anti-VEGF therapies in other indications regarded a difference of 5 letters as clinically relevant. For example, the CATT study in AMD, comparing ranibizumab and bevacizumab in a setting close to real life, used a non-inferiority margin of 5 letters in the in BCVA (CATT Research Group 2011).

Recently, controlled Phase-3 clinical trials studying AMD (HARBOR study [Ho et al. 2014]) or DME (RETAIN study [Campochiaro et al. 2014]) were based on a reduced margin of 4 letters.

In line with this consideration, the present study uses a non-inferiority margin of 4 letters. It should be noted that the RETAIN trial used a slightly different primary endpoint (mean *average* change of BCVA) than this study. Using the same margin for this study which employs the mean change of BCVA *at Week 52* as primary endpoint, is more conservative than the precedence set by RETAIN.

Missing data / drop outs

To be consistent with the pivotal Phase-3 studies for this indication, missing BCVA values will be imputed using the (last observation carried forward [LOCF]) approach.

The following other methods will be applied to account for missing data (assuming that the missing values are missing at random):

1. Multiple imputations
2. Repeated measurements model

Moreover, an observed-case analysis will be provided.

10.3.2.2.2 Secondary efficacy variables

The secondary efficacy variables are:

- Change from baseline in ETDRS BCVA letter score for the study eye to Week 100
- Change from baseline in CRT in the study eye to Week 52
- Change from baseline in CRT in the study eye to Week 100

The secondary variables will be analyzed descriptively only, i.e. no confirmatory hypothesis testing will be performed. However, the same model as outlined for the primary efficacy variable will be applied to calculate confidence intervals for the differences between the flexible regimen and the 2Q8fix group.

10.3.2.2.3 Exploratory efficacy variables

All exploratory efficacy variables will be analyzed descriptively. Confidence intervals for the differences between the flexible regimen and the 2Q8fix group will be provided where appropriate.

10.3.2.3 Safety analyses

All safety variables will be summarized descriptively on the SAF.

10.3.2.3.1 Adverse events

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. Non-ocular, ocular AEs in the study eye, and non-ocular AEs in the fellow eye will be displayed separately.

Potential arterial thrombotic events (ATEs) as described in Section 9.6.1.3 will be presented separately.

10.3.2.3.2 Other safety variables

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

10.4 Determination of sample size

Sample size determination is based on the following assumptions:

(i) The following standard deviations for the change in BCVA from randomization to Week 52
- 2Q8fix regimen: 9
- 2Q8ext regimen: 11
- 2PRN regimen: 11

(ii) Non-inferiority margin of 4 letters

(iii) Equal mean change in BCVA from study baseline to Week 52 in the treatment groups

(iv) Family wise error rate (for the two comparisons) alpha of 2.5% (one-sided tests).

The sample size estimation resulted in 135 evaluable subjects per treatment group (calculated with PASS 11, non-inferiority of two means) to reach a power of ~90% to obtain a significant result for the comparison of 2Q8ext vs. 2Q8fix (for the comparison of 2PRN vs. 2Q8fix).

With an expected drop-out rate of approximately 17%, a total of approximately 490 subjects should be randomized (163 per treatment group) to ensure a sufficient power also in the PPS analysis.

10.5 Planned interim analyses

No formal interim analysis will be conducted.

The primary endpoint data will be analyzed at Week 52 and will serve as basis for the clinical study report to be written at this point, while the final analysis of the Week-100 data will be conducted at that point.

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

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. IxRS, laboratory, adjudication committees, reading center).

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

11.4 Missing data

Most important is to avoid missing data, e.g. by monitoring in time for completeness (see Section 11.2) and investigators' training, especially to motivate subjects to be compliant with the study protocol.

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.

11.6 Archiving

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

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

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

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

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

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due 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 sponsor's medical expert is identified on the title page (including contact details).

The co-ordinating investigator responsible for signing the final clinical study report (CSR) will be assigned by the sponsor after finalization of this protocol.

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 ophthalmic images obtained by OCT and FP / FA, as described in Section 9.4.1.2 and Section 9.4.1.6, respectively.

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 committee, the functional roles, and responsibilities will be specified in its 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 and Regulatory Affairs as appropriate.

Finally, an adjudication committee will perform an additional analysis of arterial thrombotic events (ATEs) as described in Section 10.3.2.3.1. The composition of the committee, the functional roles, and responsibilities are specified in its 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

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.

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions.

Only if the subject / legal representative or proxy consenter 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 subject'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.

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

The informed consent form and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative or proxy consenter 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.

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

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15. Protocol amendments

not applicable for the original protocol

16. Appendices

16.1 NEI VFQ-25 Questionnaire

PB/IA

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

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

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.