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Official Title:	Open-label Phase-4 study to examine the change of vision-related quality of life in subjects with diabetic macular edema (DME) during treatment with intravitreal injections of 2 mg aflibercept according to EU label for the first year of treatment
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Open-label Phase-4 study to examine the change of vision-related quality of life in subjects with diabetic macular edema (DME) during treatment with intravitreal injections of 2 mg aflibercept according to EU label for the first year of treatment

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

- **Original protocol**, Version 1.0, dated 10 February 2015
- **Amendment 01** (global amendment described in Section 15.1) forming integrated protocol Version 2.0, dated 07 September 2015

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

1. Title page

Open-label Phase-4 study to examine the change of vision-related quality of life in subjects with diabetic macular edema (DME) during treatment with intravitreal injections of 2 mg aflibercept according to EU label for the first year of treatment

Investigation of the change of vision-related quality of life in subjects treated with aflibercept according to EU label for DME

Test drug:	BAY 86-5321; aflibercept; Eylea		
Study purpose:	Assessment of quality of life		
Clinical study phase:	4	Date:	07 September 2015
Registration:	EudraCT: 2014-005119-17	Version no.:	2.0
Sponsor's study no.:	BAY 86-5321 /17850		
Sponsor:	**Bayer HealthCare AG, D-51368 Leverkusen, Germany**		

PPD

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: PPD

Date: 7-9-2015

Signature:

Signature of principal investigator

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

Name:

Affiliation:

Date: _____ Signature: _____

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

2. Synopsis

Title	Open-label Phase-4 study to examine the change of vision-related quality of life in subjects with diabetic macular edema (DME) during treatment with intravitreal injections of 2 mg aflibercept according to EU label for the first year of treatment
Short title	Investigation of the change of vision-related quality of life in subjects treated with aflibercept according to EU label for DME
Clinical study phase	4
Study objective(s)	Primary objective To evaluate the change in quality of life (NEI VFQ-25) in subjects with DME during the first year of treatment with aflibercept according to the EU label for DME Secondary objectives – To assess further the safety and tolerability of aflibercept in this population – To assess the change in the diabetic retinopathy severity score (DRSS) from baseline to Week 52 – To support subject recruitment for the EMA-requested post-approval efficacy study in DME
Test drug(s)	
Name of active ingredient	BAY 86-5321 / aflibercept / Eylea
Dose(s)	2 mg aflibercept administered every 8 weeks following 5 initial monthly doses
Route of administration	Intravitreal (IVT) injection
Duration of treatment	1 year
Reference drug(s)	None
Indication	Diabetic macular edema (DME)
Diagnosis and main criteria for inclusion /exclusion	1. Type-1 or -2 diabetes mellitus 2. 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 3. Decrease in vision determined to be primarily the result of DME in the study eye 4. 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.)
Study design	Single-arm, multicenter
Methodology	NEI VFQ-25 questionnaire
Type of control	NA
Data Monitoring Committee	An adjudication committee will perform an additional analysis of arterial thrombotic events (ATEs)
Number of subjects	Total of approximately 450 to 520 subjects planned to be enrolled
Primary variable(s)	Change from baseline to Week 52 in NEI VFQ-25 total score
Time point/frame of measurement for primary variable(s)	After 52 weeks of treatment
Plan for statistical analysis	All analyses will be descriptive; no hypothesis testing will be performed. 95% confidence intervals will be provided as appropriate.

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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
ANCOVA	analysis of covariance
APTC	Antiplatelet Trialists' Collaboration
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATE	arterial thrombotic event
BCVA	best corrected visual acuity
BUN	blood urea nitrogen
CHMP	Committee for Medicinal Products for Human Use
CNV	choroidal neovascularization
CRF	case record form
CRO	contract research organization
CRT	central retinal thickness
CSR	clinical study report
DME	diabetic macular edema
DR	diabetic retinopathy
DRSS	diabetic retinopathy severity score (
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
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IOP	intraocular pressure
IRB	institutional review board
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
MCID	minimal clinically important difference
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
nAMD	neovascular age-related macula degeneration
NEI VFQ	National Eye Institute Visual Function Questionnaire
OCT	optical coherence tomography
PAES	post-approval efficacy study
PDR	proliferative diabetic retinopathy
PID	patient 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
SD	standard deviation
SD-OCT	spectral domain optical coherence tomography
SmPC	Summary of Product Characteristics
SMT	safety management team
SOC	system organ class
SUSAR	suspected, unexpected, serious adverse reaction
UPCR	urine protein/creatinine ratio
VA	visual acuity
VEGF	vascular endothelial growth factor
VIVID (DME)	A randomized, double masked, active controlled, phase III study of the efficacy and safety of repeated doses of intravitreal VEGF Trap-Eye in subjects with diabetic macular edema
VISTA (DME)	A double- masked, randomized, active-controlled, Phase 3 study of the efficacy and safety of intravitreal administration of VEGF Trap-Eye in patients with diabetic macular edema
VRQoL	vision-related quality of life
WHODD	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.

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

The detrimental impact on quality of life (QoL) from vision loss compounds any loss in QoL due to diabetes or its complications and comorbidities. This combined with the threat of further declines in visual function, or uncertain prospect of an uncomfortable treatment, may affect patients' psychological state or lead to social isolation (Droege et al. 2014; Lloyd et al. 2013)

Among the several condition-specific measures or instruments which are designed to capture the specific impact of vision loss on health-related quality of life (HRQoL) is the National Eye Institute Visual Function Questionnaire (NEI VFQ-25). This is probably the most widely used and researched instrument of this type, measuring vision-related quality of life (VRQoL) (Lloyd 2013, Mangione 2001). It was used in the pivotal trials for DME (VIVID DME and VISTA DME). The generic HRQoL measure, EQ-5D, also included in VIVID and VISTA, is now known to be unable to distinguish between different severity levels in patients with DR (Tosh et al. 2012).

3.2 Rationale of the study

Little is known about (i) QoL outcomes in DME patients treated with aflibercept per the European SmPC, or (ii) the relative influence of the visual acuity of better- and worse-seeing eyes on QoL in such patients.

Clinicians and others can use the results of studies in which QoL has been assessed to understand better how diabetes and its treatment affects outcomes that are important to

patients, and understand motivations for continuing treatment (Speight et al. 2009). Therefore, it is important to measure patients' ability to function and complete their usual activities (vision-related quality of life, VRQoL), as this may represent an important element of QoL in patients with DME that may be influenced by treatment (Hirneiss 2014).

Vision in the better-seeing eye has been thought to have a stronger influence on VRQoL than that in the worse-seeing eye, although the relative strength of influence has recently come into question (Hirneiss 2014). For example, in the RESTORE trial, 12-month gains in the near and distance subscales of NEI VFQ 25, and the composite score, were generally higher in anti-VEGF-treated patients who received their treatment in their better-seeing eye rather than in their worse-seeing eye (Mitchell et al. 2013).

As per study protocol, most of the VRQoL data in the Phase-3 program (VIVID DME and VISTA DME) was obtained from patients whose (treated) study eye was their worse-seeing eye. For subjects who met study eligibility criteria in both eyes, the study protocols specified that the eye with the worse visual acuity was to be selected as the study eye. Because of this, VRQoL results may have become confounded and dominated by the vision of the better-seeing fellow eye, which was permitted to be treated with anti-VEGFs as part of any standard care administered.

The minimally difference which can be assessed as being clinically relevant is a 4 to 6 points according to Hirneiss (2014). The clinical relevance of VRQoL changes on this instrument in DME is not well known, and may differ from 4-6 points above, largely evidenced from nAMD studies. This study provides an opportunity to establish what points change in this well-used instrument may be clinically relevant for DME (e.g. like Suner et al. [2009] did for nAMD).

This study aims to systematically and prospectively collect data on VRQoL outcomes in patients with DME treated with aflibercept per the European SmPC. It also permits exploratory analyses of the relative influence of the visual acuity of better- and worse-seeing eyes on VRQoL in such patients.

A further rationale for this study is an explicit request by EMA to conduct a long-term post-approval efficacy study (PAES) with aflibercept in DME; for that study, a sufficiently large population of patients IVT pre-treated according to the aflibercept EU label is required. Subjects completing the present protocol may subsequently be enrolled into the sponsor's DME PAES.

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 in clinical practice.

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

4. Study objectives

Primary objective

To evaluate the change in quality of life (NEI VFQ-25) in subjects with DME during the first year of treatment with aflibercept according to the EU label for DME

Secondary objectives

- To assess further the safety and tolerability of aflibercept in this population
- To assess the change in the diabetic retinopathy severity score (DRSS) from baseline to Week 52
- To support subject recruitment for the EMA-requested post-approval efficacy study in DME

5. Study design

Design overview

Single-arm, multicenter study administering aflibercept according to EU label for the first year of treatment, i.e. 2 mg every 4 weeks for 5 consecutive doses, and dosing every 8 weeks thereafter.

Primary variable

The primary efficacy variable is the change in NEI VFQ-25 total score from baseline to Week 52.

Justification of the design

Open-label setting: This is a single arm study without masking requirements. Treatment in this study is according to EU label for DME.

The length of the observation period (1 year) is based on the primary-endpoint results of the pivotal DME studies (VISTA DME, VIVID DME), where most of the benefits after start of treatment with aflibercept occurred during the initial year of treatment.

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

At the discretion of the investigator, only one eye will be designated as the study eye.

6.1 Inclusion criteria - amended

A subject must meet all of the following inclusion criteria at screening and baseline 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. Willingness and ability to comply with clinic visits and study-related procedures
3. 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
    - Vasectomised 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. [1]

1 Replacement of text for inclusion criterion 3 per Amendment 1 (see Section 15.1.1.1)

4. Negative pregnancy test (urine or serum; women of childbearing potential only)
5. Signed written informed consent [2]
6. Type-1 or -2 diabetes mellitus
7. 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
8. Decrease in vision determined to be primarily the result of DME in the study eye
9. 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 - amended

A subject must not meet any of the following exclusion criteria, at screening and baseline as applicable, to be eligible for enrollment into this study. [3]

Ocular exclusion criteria (study eye)

1. Previous treatment with anti-angiogenic drugs in study eye (e.g. pegaptanib sodium, bevacizumab, ranibizumab, aflibercept) within the last 12 weeks
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 first study treatment in the study eye
7. Yttrium-aluminum-garnet capsulotomy in the study eye within 30 days before first study treatment
8. Any other intraocular surgery within 90 days of first study 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 is thought to affect central vision
11. Pre-retinal fibrosis involving the macula of the study eye

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2 Inclusion criterion 5 specified per Amendment 1 (see Section 15.1.1.2)

3 Content and order of exclusion criteria changed per Amendment 1 (see Section 15.1.1.3)

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. Filtration surgery for glaucoma in the past or likely to be needed in the future on the study eye
14. Uncontrolled glaucoma (defined as intraocular pressure [IOP] > 25 mmHg despite treatment with antiglaucoma medication) in the study eye
15. 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)
16. Significant media opacities, including cataract, in the study eye that interferes with visual acuity, fundus photography or OCT imaging.
17. Myopia of a spherical equivalent prior to any possible refractive or cataract surgery of ≥ 8 diopters in the study eye

Ocular exclusion criteria (either eye)

18. Any ocular or periocular infection in the preceding 4 weeks in either eye
19. Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye

Ocular and systemic exclusion criteria

20. Presence of any contraindications indicated in the EU commission/locally approved label for aflibercept

Systemic exclusion criteria

21. Administration of systemic anti angiogenic agents within 180 days before first study treatment
22. Uncontrolled diabetes mellitus, as defined by hemoglobin (Hb)A1c > 12.0%
23. 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)
24. Allergy or hypersensitivity to fluorescein
25. Current treatment for a serious systemic infection
26. History of either cerebral vascular accident and/or myocardial infarction within 180 days before first study treatment
27. Renal failure requiring dialysis or renal transplant

28. 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
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)
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 - amended

Withdrawal criteria

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

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

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

- The subject had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- The inclusion / exclusion criteria preventing the subject's initial attempt to participate have been changed (via protocol amendment).
- The reason for the screening failure was subsequently resolved (e.g. decrease of elevated IOP, controlled arterial hypertension) within 30 days.[4]

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.

The investigator must ensure that the repeated screening procedures do not expose the subject to an unjustifiable health risk. Also, for re-screening, the subject must 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 received at least one dose of study medication.

4 Time frame added per Amendment 1 (see Section 15.1.1.4)

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 as medically needed.

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

6.3.2 Replacement

Subjects who withdraw from the study will not be replaced.

6.4 Subject identification - amended

The subject number is a 9-digit number consisting of: [5]

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.

5 Description of subject identification number changed per Amendment 1 (see Section 15.1.1.5)

7. Treatments

7.1 Treatments to be administered

All subjects will receive aflibercept according to the EU label posology, i.e. 5 monthly intravitreal injections followed by administrations every 8 weeks.

7.2 Identity of study treatment

The identity of the study drug is summarized in Table 7–1.

Table 7–1: Identity of study drug

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

All study drug 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 drug, 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

In this single-arm study, all eligible subjects will receive aflibercept according to the EU label for DME.

7.4 Dosage and administration - amended

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

- Sterile study drug in sealed glass vials (2 mL) with a withdrawable volume of 0.1 mL (see Table 7–1 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.

Preparation of the solution

Based on present stability information, the preparation of the solution should be scheduled to ensure that the subsequent injection is completed within 2 hours of the start of the preparation.

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 must not be used for IVT injection. The filter needle should be replaced by the sterile 30-gauge needle for the IVT injection.

Dosage

For the 2-mg dose of aflibercept, the volume of injection is 50 µL (0.05 mL). Thus, the syringe contents should be expelled until the plunger is aligned with the line that marks 0.05 mL on the syringe.

Administration

Aflibercept is administered via IVT injection. The injection must be completed within 2 hours of the start of dose preparation.

Posology

All subjects enrolled in this single-arm study will be receive aflibercept according to EU label for the first year in an open-label fashion, i.e. 5 monthly intravitreal injections followed by intravitreal injections every 8 weeks.

Consideration of special warnings from EU label [6]

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.

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6 Paragraph added per Amendment 1 (see Section 15.1.1.6)

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.

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, including surgeries and laser 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 medications 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 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.

After completion of this study, subjects may subsequently be enrolled into the sponsor's post-approval efficacy study further investigating the efficacy of aflibercept in DME patients.

9. Procedures and variables

9.1 Tabular schedule of evaluations - amended

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

	Screening **Visit 1**	*Baseline* **Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7 to Visit 10**	*End of study / early termin.* **Visit 11**
Acceptable deviations relative to BL	4 weeks before BL	Day 1	Week 4 ± 5 days	Week 8 ± 5 days	Week 12 ± 5 days	Week 16 ± 5 days	Week 24 to Week 48 ±10 days [a]	Week 52c ± 10 days
Initiation procedures								
Informed consent	●							
Demographic data	●							
Medical / ophthalmic history	●							
Check of enrollment criteria	●	●						
Study medication								
Administration of study drug		●	●	●	●	●	●	no treatment
Ophthalmologic assessments	(●● = bilaterally; ●○ = study eye only [additional assessments may occur outside of this protocol])							
BCVA (ETDRS chart starting at 4 m) [b]	●●	●○	●○	●○	●○	●○	●○	●●
Optical coherence tomography	●○	●○						●○
Fluorescein angiography	●○							●○
Fundus photography	●●							●●
Indirect ophthalmoscopy [c]	●○	●○	●○	●○	●○	●○	●○	●○
Slit lamp biomicroscopy [7]	●●	●●	●○	●○	●○	●○	●○	●○
Intraocular pressure (IOP) [c]	●○	●○	●○	●○	●○	●○	●○	●○
Patient-reported outcomes								
NEI VFQ-25	●	●	●	●	●	●	●	●
Standard safety								
Prior / concomitant medications	●	●	●	●	●	●	●	●
Adverse events [d]	●	●	●	●	●	●	●	●
Hematology / chemistry	●							●
Urinalysis / UPCR	●							●
Pregnancy test - serum [e] [8] (women of childbearing potential only)	●							
Pregnancy test – urine dipstick (women of childbearing potential only) [f]		●						●
Vital signs (body temperature, blood pressure, pulse)	●	●						●

BCVA = best corrected visual acuity; BL = baseline; ETDRS = Early Treatment Diabetic Retinopathy Study; UPCR = urine protein / creatinine ratio

Footnotes to table on next page

7 Changed to bilaterally for screening and baseline per Amendment 1 (see Section 15.1.1.7)

8 Urine dipstick no alternative to serum test per Amendment 1 (see Section 15.1.1.9)

Footnotes to Table 9–1 [9]

a The intervals between Visits 6 to 9 are 8 weeks ±10 days.
The interval between Visit 9 and Visit 10 must be ≥ 56 days (8 weeks).

b Refraction to be done at each visit

c Also post injection

d 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).

e The test is to take place within 7 days before the first injection of study medication [10]

f The test is to be repeated as frequently as required [11]

9 Footnotes re-arranged per Amendment 1 (see Section 15.1.1.8)

10 Footnote added per Amendment 1 (see Section 15.1.1.10)

11 Footnote changed per Amendment 1 (see Section 15.1.1.11)

9.2 Visit description

9.2.1 Visit 1 - Screening - amended

Scheduling

The Screening visit must occur within 4 weeks of the baseline visit (Day 1).

Conduct

The following procedures will be performed at this visit:

- Collection of 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 9 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)
- NEI VFQ-25 (see Section 9.4.1 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
- Serum pregnancy test in women of childbearing potential [12]
- Vital signs (body temperature, blood pressure and pulse) (see Section 9.6.3.2 for details)

12 Urine dipstick test no alternative to serum test at screening per in Amendment 1 (see Section 15.1.1.9)

9.2.2 Visit 2 (Day 1) - Baseline - amended

Scheduling

This visit should take place within 4 weeks of the screening visit.

Conduct

The following procedures will be performed at this visit:

- Assessment of inclusion and exclusion criteria (see Sections 6.1 and 9 for details)
  - Including urine dip stick pregnancy test for women of childbearing potential [13]
- Record of concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Pre-injection 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)
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intraocular pressure (IOP)
- NEI VFQ-25 (see Section 9.4.1 for details)
- Vital signs (body temperature, blood pressure and pulse) (see Section 9.6.3.2 for details)
- First application of study medication (see Section 7.4 for details)
  Injections are to take place *after* completion of the procedures listed above.
- Post-injection ocular assessments (see Section 9.4.1 for details):
  - Indirect ophthalmoscopy
  - Intraocular pressure (IOP)

13 Urine dipstick test added for baseline visit per Amendment 1 (see Section 15.1.1.9)

9.2.3 Visit 3 to Visit 10 (Week 4 to Week 48)

Scheduling

For the scheduling of these visits, the following deviations relative to baseline are acceptable:

- Monthly post-baseline visits through week 16 (Visits 3 to 6): ± 5 days
- Regular Q8 schedule (Visits 7 to 9) ± 10 days
- The interval between Visit 9 and Visit 10 must be at least 56 days (8 weeks).

Conduct

The conduct of Visit 3 to Visit 10 will be identical. The following procedures will be performed at these visits:

- Record of concomitant medications (see Section 8.1 for details)
- Record of adverse events (see Section 9.6.1 for details)
- Pre-injection 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
  - Slit lamp biomicroscopy
  - Intraocular pressure (IOP)
- NEI VFQ-25 (see Section 9.4.1 for details)
- Application of study medication (see Section 7.4 for details)
  Injections are to take place *after* completion of the procedures listed above.
- Post-injection ocular assessments (see Section 9.4.1 for details):
  - Indirect ophthalmoscopy
  - Intraocular pressure (IOP)

9.2.4 Visit 11 (Week 52) - Final visit or early termination

Scheduling

This visit will be the last scheduled visit under this protocol. It is to be scheduled at Week 52 (± 10 days) after baseline.

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

Conduct

At this visit, no study medication under this protocol will be administered.

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)
  - Fundus photography (FP) and fluorescein angiography (FA)
  - Indirect ophthalmoscopy
  - Slit lamp biomicroscopy
  - Intraocular pressure (IOP)
- 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 dipstick test) [14]
- Vital signs (body temperature, blood pressure and pulse) (see Section 9.6.3.2 for details)
- NEI VFQ-25 (see Section 9.4.1 for details)

14 Urine dipstick test only per Amendment 1 (see Section 15.1.1.11)

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 - amended

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

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 and life style details including smoking history will be recorded. [15]

15 Recording of smoking history added per Amendment 1 (see Section 15.1.1.12)

9.4 Efficacy - amended

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

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. [16]

9.4.2 Ophthalmic examinations

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

Unless otherwise specified, all ophthalmic evaluations under this protocol will be conducted on the study eye only according to the schedule detailed in Section 9.1 (Table 9–1). At any visit, ophthalmic examinations not stipulated by this protocol may take place outside of this protocol at the discretion of the investigator.

All ophthalmic evaluations are to be performed before study drug injection. In addition, indirect ophthalmoscopy and IOP measurement are also to be performed post injection.

The investigator will record all variables as specified in the CRF.

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

9.4.2.1 Best corrected visual acuity (BCVA)

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. Examiners of visual acuity (VA) must be certified to ensure consistent measurement of BCVA. Unilateral versus bilateral examinations are specified in Table 9–1 for each visit. A detailed protocol for conducting VA testing and refraction can be found in the Study Manual.

16 Documentation of name added per Amendment 1 (see Section 15.1.1.14)

9.4.2.2 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 electronically archived at the study sites as part of the source documentation.

9.4.2.3 Indirect ophthalmoscopy

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

9.4.2.4 Slit lamp biomicroscopy

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

9.4.2.5 Intraocular pressure (IOP)

IOP is to be measured using applanation tonometry (Goldmann, Tonopen or approved alternative). 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).

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

The anatomical state of the retinal vasculature of the study eye will be evaluated by funduscopic examination, FP and FA. Fundus and angiographic images will be read by the investigator. All FA and FP images will be archived electronically [17] at the site as part of the source documentation.

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

9.4.3 Efficacy variables

All efficacy variables derived from the ophthalmic examinations are specified in Section 10.3.1.1. [18]

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17 Clarification for archiving as electronic archiving added per Amendment 1 (see Section 15.1.1.15)

18 Section added per Amendment 1 (see Section 15.1.1.13)

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 reduced

– 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 "fatal" of underlying AE(s).

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

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

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

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

ATE analysis

Potential arterial thrombotic events (ATEs) will be evaluated by an 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 - amended

Information on AEs with an onset after the first application of the test drug is provided in the local label. [19]

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

9.6.2 Pregnancies - amended

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

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

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

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

Results from animal studies with high systemic exposure indicate that aflibercept can impair male and female fertility. Such effects are not expected after ocular administration with very low systemic exposure. [20]

19 Sentence revised per Amendment 1 (see Section 15.1.1.16)

20 Paragraph added per Amendment 1 (see Section 15.1.1.17)

9.6.3 Further safety

9.6.3.1 Laboratory evaluations - amended

Laboratory evaluation will be conducted according to the schedule provided in Section 9.1 (beyond that schedule, pregnancy tests are to be done in women of childbearing potential as outlined in Table 9–1). [21]

Blood will be drawn before FA by direct venipuncture.

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

The date 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 9–2: Laboratory safety parameters - amended

Chemistry	Urinalysis	Hematology
Sodium	Glucose	Hemoglobin
Potassium	Protein	Hematocrit
Chloride	Specific Gravity	Red blood cell count
Calcium	Blood	Mean corpuscular volume (MCV)
Glucose	Ketones	Mean corpuscular hemoglobin concentration (MCHC)
HbA1c	Protein:Creatinine Ratio (UPCR)	Mean corpuscular hemoglobin (MCH)
Albumin		Leucocyte count
Total Protein, Serum	Pregnancy test for women of childbearing potential (see Table 9–1)	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 [22]		
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.

21 Scheduling of serum and urine pregnancy test changed per Amendment 1 (see Section 15.1.1.11)

22 Total and HDL cholesterol added per Amendment 1 (see Section 15.1.1.18)

9.6.3.2 Vital signs (body 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 as well as further details of the analysis 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 subjects who received at least one injection of study drug *and* have completed the baseline and at least one post-baseline NEI VFQ-25 questionnaire.

The **Safety Analysis Set** will include all subjects who have received at least one injection of study drug.

10.3 Variables and planned statistical analyses

10.3.1 Variables

10.3.1.1 Efficacy variables

Primary efficacy variables

The primary efficacy variable is

- The change from baseline to Week 52 in the NEI VFQ-25 total score

The calculation for NEI VFQ-25 sub-scale scores and total score will be performed according to the "NEI VFQ-25 Scoring Algorithm – August 2000".

Secondary efficacy variables

The secondary efficacy variables include

- The change from baseline to Week 52 in the NEI VFQ-25 near activities subscale
- The change from baseline to Week 52 in the NEI VFQ-25 distant activities subscale
- The change from baseline to Week 52 in BCVA (ETDRS letter score)
- The change from baseline to Week 52 in CRT measured by OCT
- Proportion of subjects progressing to ≥ 61 ETDRS diabetic retinopathy severity scale (DRSS) as assessed by FP

Exploratory efficacy variables

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 (see Section 9.6.1)
- Vital signs (see Section 9.6.3.2)
- Ophthalmologic safety variables (see Section 9.4.1)

10.3.2 Statistical and analytical plans

10.3.2.1 Demography and baseline characteristics - amended

Demographic variables and baseline characteristics will be summarized for both [23] analysis sets, 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.

10.3.2.2 Efficacy analyses

All efficacy variables will be analyzed on the FAS.

Primary efficacy variable

The analyses of the primary efficacy variable will be descriptively. 95% confidence intervals will be provided based on the t-distribution assuming that the changes from baseline are normally distributed.

To be comparable with publications of other studies in this indication, missing values will be imputed with the last observed post-baseline value collected before the missing value (LOCF).

Frequencies of subjects worsening or improving (separately for not achieving, achieving or exceeding the clinically meaningful difference specified in Section 10.4) will be computed for each time point.

With regard to the classification of clinical meaningfulness of QoL at Week 52, mean change in BCVA will be calculated for each of the two categories. The difference in mean change in BCVA between the two categories of clinically meaningfulness of QoL will be evaluated, together with t-distribution-based 95% confidence intervals.

As sensitivity analysis a multiple imputation (MI) analysis will be provided. The imputations will be based on the baseline value as well as all observed changes from baseline.

Furthermore, a repeated-measurements-model analysis will be conducted including the visit as fixed factor and the baseline value and the baseline*visit interaction as covariate.

In addition, the effect of the choice of the study eye on the quality of life (better seeing eye vs. worse seeing eye) will be investigated.

Further exploratory analyses will be conducted to investigate the intra-individual variability in the score over time and the correlation between the BCVA value in both eyes and the score.

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23 Correction from 3 to 2 analysis sets per Amendment 1 (see Section 15.1.1.19)

Secondary efficacy variables

The secondary efficacy variables will be analyzed descriptively in analogy to the primary efficacy variables.

Exploratory efficacy variables

All exploratory variables will be analyzed descriptively.

10.3.2.3 Safety analyses - amended

All safety variables will be summarized descriptively on the SAF.

Adverse events

Treatment-emergent AEs will be presented by MedDRA preferred term within primary system organ class (SOC). [24] 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.

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

A total of approximately 450 to 520 subjects is planned to be enrolled. This takes the sponsor's planned subsequent post-approval efficacy study into consideration.

In a previously conducted study with aflibercept in DME, the standard deviation observed for the change from baseline to Week 52 in the NEI VFQ-25 total score was 11.

Assuming a similar variability (SD = 11), with a sample size of 450 subjects (520 subjects), the difference between the mean and the limits of the 95% confidence intervals will not exceed 1.1 (1.0) with a probability of 90%.

24 No summary by treatment groups per Amendment 1 (see Section 15.1.1.20)

As the minimal clinically important difference (MCID) has been reported to be in the range of 4 to 6 (Hirneiss 2014), for the context of this study, it was decided to use the value of 5 as MCID. The change in QoL will be classified according to the two categories

- Change ≥ MCID
- Change < MCID (this includes no change or deteriorations).

In both categories, the mean change from baseline in BCVA will be evaluated, and a 95% confidence interval for the difference between both categories will be calculated. Taken the sample size range specified above and assumptions[25] for the distribution of subjects on the two MCID categories, the length of this respective confidence interval will not exceed 1.8 to 1.9 letters with a probability of 90% (with SD = 10 for change in BCVA based on previously conducted studies with aflibercept in DME).

This precision is considered to be sufficient to assess the relevance of change in QoL over time, and in relation to BCVA measurements.

Sample size calculated with PASS (Power Analysis & Sample Size) v. 11 (Confidence Intervals for One Mean with Tolerance Probability and Confidence Intervals for the Difference Between Two Means with Tolerance Probability).

10.5 Planned interim analyses

No formal interim analysis will be conducted.

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 (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/CRO has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer/CRO 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/CRO extensively

25 Based on former aflibercept in DME studies, and considering the slightly different population in this study, a proportion between 50:50 and 70:30 is assumed.

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 the sponsor'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. 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 screen failure
- 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, adjudication committees).

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

11.4 Missing data

All efforts will be made to minimize the amount of missing data. Measures for this include investigators' training and timely monitoring of CRF entries for completeness (see Section 11.2).

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.

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

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

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

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

12. Premature termination of the study

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

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of 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.

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 IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

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

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

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

13.4 Subject information and consent - amended

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject, prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data are 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 early-termination examinations as specified in the visit description described in Section 9.2.4 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. [26]

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 patient's note/file of the medical institution.

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

If the subject is unable to read the informed consent form due to vision impairment, a family member, other legal representative of the subject, study nurse, or study physician may read the document to the subject and may assist the subject in signing the form. In this case, the name of that person should be documented. [27]

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.

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26 Paragraph revised to align with sponsor internal standards per Amendment 1 (see Section 15.1.1.21)

27 Paragraph added to align with sponsor internal standards per Amendment 1 (Section 15.1.1.21)

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

Editorial note

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

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

Correction of typos or omissions are not highlighted.

15.1 Amendment 1, dated 07 September 2015

15.1.1 Overview of changes to the study

15.1.1.1 Modification 1 - Inclusion criterion 3

Inclusion criterion 3 - use of adequate contraception (definition based on the judgment of the investigator) replaced with use of highly effective contraception (definition based on CTFG from 15 SEP 2014).

Rationale: For subject safety reasons

The following protocol sections are affected by this modification:

- Section 6.1 Inclusion criteria

15.1.1.2 Modification 2 –Inclusion criterion 5

'Written informed consent' complemented by 'signed'

Rationale: Specification of informed consent

The following protocol sections are affected by this modification:

- Section 6.1 Inclusion criteria

15.1.1.3 Modification 3 – Exclusion criteria

Content and order of exclusion criteria changed.

Rationale: More detailed specification, clearer overview

The following protocol sections are affected by this modification:

- Section 6.2 Exclusion criteria

15.1.1.4 Modification 4 – Re-screening criteria

Time frame for resolution of reason for screening failure (to allow re-screening) added to list of criteria for re-screening.

Rationale: Clarification

The following protocol sections are affected by this modification:

- Section 6.3.1 Withdrawal

15.1.1.5 Modification 5 – Subject identification number

Description of subject identification number changed.

Rationale: Correction

The following protocol sections are affected by this modification:

- Section 6.4 Subject identification

15.1.1.6 Modification 6 – EU SmPC update

Special warnings from EU SmPC (most recent version number) added to dosage and administration.

Rationale: For subject safety reasons

The following protocol sections are affected by this modification:

- Section 7.4 Dosage and administration

15.1.1.7 Modification 7 – Slit lamp biomicroscopy in schedule of evaluations

Description of slit lamp biomicroscopy updated.

Rationale: In agreement with exclusion criteria 18 and 19 to be performed bilaterally at screening and baseline

The following protocol sections are affected by this modification:

- Section 9.1 Tabular schedule of evaluations

15.1.1.8 Modification 8 – Order of footnotes in schedule of evaluations

Arranging the footnotes in the order the table is read, line by line

Rationale: More reader friendly

The following protocol sections are affected by this modification:

- Section 9.1 Tabular schedule of evaluations

15.1.1.9 Modification 9 – Specification of pregnancy testing

Serum test binding for screening visit (urine dipstick is no alternative); urine dipstick test added for baseline visit

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

The following protocol sections are affected by this modification:

- Section 9.1 Tabular schedule of evaluations
- Section 9.2.1 Visit 1 - Screening
- Section 9.2.2 Visit 2 (Day 1) - Baseline

15.1.1.10 Modification 10 – Footnote in schedule of evaluations

- Footnote e (part of former d, see Modification 9, Section 15.1.1.9) Serum pregnancy test within 7 days before first injection of study medication

Rationale: For subject safety reasons

The following protocol sections are affected by this modification:

- Section 9.1 Tabular schedule of evaluations

15.1.1.11 Modification 11 – Timing of pregnancy testing

Footnote f (part of former d, see Modification 9, Section 15.1.1.9) 'The [urine dipstick pregnancy] test is to be repeated as frequently as required' and is required at Visit 11 (final visit or early termination)

Rationale: For subject safety reasons

The following protocol sections are affected by this modification:

- Section 9.1 Tabular schedule of evaluations
- Section 9.2.4 Visit 11 (Week 52) - Final visit or early termination
- Section 9.6.3.1 Laboratory evaluations

15.1.1.12 Modification 12 – Smoking history

Addition of smoking history to the medical history

Rationale: The smoking history was added to allow analysis of the general cardiovascular risk

The following protocol sections are affected by this modification:

- Section 9.3.2 Medical/surgical and ophthalmic history

15.1.1.13 Modification 13 – Efficacy variables

New sub-section 9.4.3 Efficacy variables added to Section 9.4 Efficacy

Rationale: Reference to Section 10.3.1.1 regarding efficacy variables derived from the ophthalmic examinations

The following protocol sections are affected by this modification:

- Section 9.4 Efficacy

15.1.1.14 Modification 14 – NEI VFQ-25 questionnaire

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

Rationale: Clarification of process

The following protocol sections are affected by this modification:

- Section 9.4.1 National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25)

15.1.1.15 Modification 15 – Archiving of FA and PP images

Requirement to archive FA and FP images electronically added.

Rationale: Clarification

The following protocol sections are affected by this modification:

- Section 9.4.2.6 Fundus photography (FP) and fluorescein angiography (FA)

15.1.1.16 Modification 16 – Expected adverse events

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

Rationale: Editorial clarification of the process

The following protocol sections are affected by this modification:

- Section 9.6.1.5 Expected adverse events

15.1.1.17 Modification 17 – Reporting of pregnancies

New paragraph on fertility added to Section 9.6.2 Pregnancies

Rationale: To include guidance in a specific adverse event situation

The following protocol sections are affected by this modification:

- Section 9.6.2 Pregnancies

15.1.1.18 Modification 18 – Laboratory safety parameters

Addition of total and HDL cholesterol to the laboratory safety parameters.

Rationale: Total cholesterol and HDL cholesterol were added to allow analysis of the general cardiovascular risk

The following protocol sections are affected by this modification:

- Section 9.6.3.1 Laboratory evaluations

15.1.1.19 Modification 19 – Analysis sets for demographiy and baseline characteristics

Three analysis sets changed to two

Rationale: Correction

The following protocol sections are affected by this modification:

- Section 10.3.2.1 Demography and baseline characteristics

15.1.1.20 Modification 20 – Safety analysis

Summary by treatment groups removed.

Rationale: Only 1 treatment group

The following protocol sections are affected by this modification:

- Section 10.3.2.3 Safety analyses

15.1.1.21 Modification 21 – Subject information and consent process

Revision of text describing the subject information and informed consent process

Rationale: Alignment with sponsor internal standards

The following protocol sections are affected by this modification:

- Section 13.4 Subject information and consent

15.1.1.22 Modification 22 – Replacement of patients with subjects

“Patients” replaced with “subjects” where applicable

Rationale: To establish consistency in wording throughout the text

- This terminological change is not marked as change in the text.

15.1.2 Changes to the protocol text

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

The addition of HDL and HRQoL to the list of abbreviations is not highlighted additionally in this section.

Section 6.1 Inclusion criteria

Inclusion criterion 3 replaced per Modification 1 (Section 15.1.1.1).

Old text:

3. ~~Women and men of reproductive potential must agree to use adequate contraception when sexually active. This applies for the time period between signing of the informed consent form and 3 months after the last administration of study drug.~~

   ~~The definition of adequate contraception will be based on the judgment of the investigator and on local requirements.~~

   ~~Acceptable methods of contraception include, but are not limited to: (i) condoms (male or female) with or without a spermicidal agent; (ii) diaphragm or cervical cap with spermicide; (iii) intra-uterine device; (iv) hormone-based contraception.~~

   ~~Subjects must agree to utilize two reliable and acceptable methods of contraception simultaneously.~~

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

New text:

3. 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
    - Vasectomised 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.

Section 6.1 Inclusion criteria

Inclusion criterion 5 changed per Modification 2 (Section 15.1.1.2).

Old text:

5. Written informed consent

New text:

5. Signed written informed consent

Section 6.2 Exclusion criteria

Content and order of exclusion criteria changed per Modification 3 (Section 15.1.1.3).

Old text:

A subject must not meet any of the following exclusion criteria, at screening and baseline as applicable, to be eligible for enrollment into this study.

1. Previous treatment with anti-angiogenic drugs in study eye (e.g. pegaptanib sodium, bevacizumab, ranibizumab) within the last 12 weeks
2. History of vitreoretinal surgery and/or including scleral buckling in the study eye
3. ~~Use of~~ long acting steroids, either periocular or intraocular, in the preceding 120 days
4. Any ocular or periocular infection in the preceding 4 weeks
5. Active proliferative diabetic retinopathy (PDR), current iris neovascularization, vitreous hemorrhage, or tractional retinal detachment in the study eye
6. Aphakia in the study eye
7. Cataract surgery within 90 days
8. Yttrium-aluminum-garnet capsulotomy in the study eye within 30 days
9. Any other intraocular surgery within 90 days
10. Ocular inflammation (including trace or above) or history of uveitis in the study eye
11. Vitreomacular traction or epiretinal membrane in the study eye evident biomicroscopically or on OCT that is thought to affect central vision
12. Pre-retinal fibrosis involving the macula of the study eye
13. 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
14. Filtration surgery for glaucoma in the past or likely to be needed in the future on the study eye

~~15. Intraocular pressure (IOP) ≥ 25 mmHg in the study eye~~

16. 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 retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization of any cause)
17. Myopia of a spherical equivalent prior to any possible refractive or cataract surgery of ≥ 8 diopters
18. Administration of systemic anti angiogenic agents within 180 days

Uncontrolled diabetes mellitus in the opinion of the investigator

19. 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)
20. Presence of any contraindications indicated in the EU commission/locally approved label for aflibercept
21. Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye
22. Allergy to fluorescein
23. Current treatment for a serious systemic infection
24. History of either cerebral vascular accident and/or myocardial infarction within 180 days
25. Renal failure requiring dialysis or renal transplant
26. 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
27. Significant media opacities, including cataract, in the study eye that interferes with visual acuity, fundus photography or OCT imaging.
28. Breast-feeding women
29. ~~Previous assignment to treatment during this study~~
30. Concomitant participation in another clinical study with investigational medicinal product(s).
31. 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)

New text:

A subject must not meet any of the following exclusion criteria, at screening and baseline as applicable, to be eligible for enrollment into this study.

Ocular exclusion criteria (study eye)

1. Previous treatment with anti-angiogenic drugs in study eye (e.g. pegaptanib sodium, bevacizumab, ranibizumab) within the last 12 weeks
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 first study treatment in the study eye
7. Yttrium-aluminum-garnet capsulotomy in the study eye within 30 days before first study treatment
8. Any other intraocular surgery within 90 days of first study 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 is 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. Filtration surgery for glaucoma in the past or likely to be needed in the future on the study eye
14. Uncontrolled glaucoma (defined as intraocular pressure [IOP] ≥ 25 mmHg despite treatment with antiglaucoma medication) in the study eye
15. 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)
16. Significant media opacities, including cataract, in the study eye that interferes with visual acuity, fundus photography or OCT imaging.
17. Myopia of a spherical equivalent prior to any possible refractive or cataract surgery of ≥ 8 diopters in the study eye

Ocular exclusion criteria (either eye)

18. Any ocular or periocular infection in the preceding 4 weeks in either eye
19. Evidence of infectious blepharitis, keratitis, scleritis, or conjunctivitis in either eye

Ocular and systemic exclusion criteria

20. Presence of any contraindications indicated in the EU commission/locally approved label for aflibercept

Systemic exclusion criteria

21. Administration of systemic anti angiogenic agents within 180 days before first study treatment
22. Uncontrolled diabetes mellitus as defined by hemoglobin (Hb)A1c > 12.0%
23. 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)
24. Allergy or hypersensitivity to fluorescein
25. Current treatment for a serious systemic infection
26. History of either cerebral vascular accident and/or myocardial infarction within 180 days before first study treatment
27. Renal failure requiring dialysis or renal transplant
28. 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
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).
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)

Section 6.3.1 Withdrawal

Criteria for re-screening clarified as per Modification 4 (Section 15.1.1.4)

Old text:

Screening failure

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

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

- The subject had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- The inclusion / exclusion criteria preventing the subject's initial attempt to participate have been changed (via protocol amendment).

The reason for the screening failure was subsequently resolved (e.g. decrease of elevated IOP, controlled arterial hypertension).

New text:

Screening failure

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

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

- The subject had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- The inclusion / exclusion criteria preventing the subject's initial attempt to participate have been changed (via protocol amendment).

The reason for the screening failure was subsequently resolved (e.g. decrease of elevated IOP, controlled arterial hypertension) within 30 days.

Section 6.4 Subject identification

Description of subject identification number changed per Modification 5 (Section 15.1.1.5).

Old text:

The subject number is a 9 digit number consisting of:

~~Digits 1 to 2 = Country code~~

~~Digits 3 to 5 = Center number within the country~~
~~(Digits 1 to 5 = Trial unit)~~

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

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.

New text:

The subject number is a 9-digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current subject number within the center

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

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

Section 7.4 Dosage and administration

Following paragraph added below 'Posology' per Modification 6 (Section 15.1.1.6).

Consideration of special warnings from EU label

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

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

> Treatment should be withheld in patients with rhegmatogenous retinal detachment or stage 3 or 4 macular holes. In the event of a retinal break, the dose should be withheld and treatment should not be resumed until the break is adequately repaired.
>
> The dose should be withheld and treatment should not be resumed earlier than the next scheduled treatment in the event of:
>
> - a decrease in 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

Section 9.1 Tabular schedule of evaluations

Slit lamp biomicroscopy updated as per Modification 7 (Section 15.1.1.7).

Footnotes re-arranged per Modification 8 (Section 15.1.1.8).

Pregnancy test: Serum test binding for screening visit, urine dipstick test added for baseline visit per Modification 9 (Section 15.1.1.9).

Footnote e, serum pregnancy test within 7 days before first injection of study medication added per Modification 10 (Section 15.1.1.10).

Footnote f (former d, see Modification 8, Section 15.1.1.8) urine dipstick pregnancy test is to be repeated as frequently as required changed per Modification 11 (Section 15.1.1.11)

Old text:

Table 9-1: Schedule of assessments and procedures

Acceptable deviations relative to BL	*Screening* **Visit 1** 4 weeks before BL	*Baseline* **Visit 2** Day 1	**Visit 3** Week 4 ± 5 days	**Visit 4** Week 8 ± 5 days	**Visit 5** Week 12 ± 5 days	**Visit 6** Week 16 ± 5 days	**Visit 7 to Visit 10** Week 24 to Week 48 ±10 days[e]	*End of study / early termin.* **Visit 11** Week 52c ± 10 days
Initiation procedures								
Informed consent	●							
Demographic data	●							
Medical / ophthalmic history	●							
Check of enrollment criteria	●	●						
Study medication								
Administration of study drug		●	●	●	●	●	●	no treatment
Ophthalmologic assessments	(●● = bilaterally; ●○ = study eye only [additional assessments may occur outside of this protocol])							
BCVA (ETDRS chart starting at 4 m) [a]	●●	●○	●○	●○	●○	●○	●○	●●
Optical coherence tomography	●○	●○						●○
Fluorescein angiography	●○							●○
Fundus photography	●●							●●
Indirect ophthalmoscopy [b]	●○	●○	●○	●○	●○	●○	●○	●○
Slit lamp biomicroscopy	●○	●○	●○	●○	●○	●○	●○	●○
Intraocular pressure (IOP) [b]	●○	●○	●○	●○	●○	●○	●○	●○
Patient-reported outcomes								
NEI VFQ-25	●	●	●	●	●	●	●	●
Standard safety								
Prior / concomitant medications	●	●	●	●	●	●	●	●
Adverse events [c]	●	●	●	●	●	●	●	●
Hematology / chemistry	●							●
Urinalysis / UPCR	●							●
Pregnancy test – ~~urine or~~ serum [d]	●							●
Vital signs (body temperature, blood pressure, pulse)	●	●						●

BCVA = best corrected visual acuity; BL = baseline; ETDRS = Early Treatment Diabetic Retinopathy Study; UPCR = urine protein / creatinine ratio

a: Refraction to be done at each visit

b Also post injection

c: 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).

d: ~~In women of childbearing potential only. The first test is to be done as close as possible before the first injection of study medication.~~ The test is to be repeated as frequently as ~~demanded by local requirements~~.

e The intervals between Visits 6 to 9 are 8 weeks ±10 days.
The interval between Visit 9 and Visit 10 must be ≥ 56 days (8 weeks).

New text:

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

Acceptable deviations relative to BL	*Screening* **Visit 1** 4 weeks before BL	*Baseline* **Visit 2** Day 1	**Visit 3** Week 4 ± 5 days	**Visit 4** Week 8 ± 5 days	**Visit 5** Week 12 ± 5 days	**Visit 6** Week 16 ± 5 days	**Visit 7 to Visit 10** Week 24 to Week 48 ±10 days[a]	*End of study / early termin.* **Visit 11** Week 52c ± 10 days
Initiation procedures								
Informed consent	●							
Demographic data	●							
Medical / ophthalmic history	●							
Check of enrollment criteria	●	●						
Study medication								
Administration of study drug		●	●	●	●	●	●	no treatment
Ophthalmologic assessments	(●● = bilaterally; ●○ = study eye only [additional assessments may occur outside of this protocol])							
BCVA (ETDRS chart starting at 4 m) [b]	●●	●○	●○	●○	●○	●○	●○	●●
Optical coherence tomography	●○	●○						●○
Fluorescein angiography	●○							●○
Fundus photography	●●							●●
Indirect ophthalmoscopy [c]	●○	●○	●○	●○	●○	●○	●○	●○
Slit lamp biomicroscopy	●●	●●	●○	●○	●○	●○	●○	●○
Intraocular pressure (IOP) [c]	●○	●○	●○	●○	●○	●○	●○	●○
Patient-reported outcomes								
NEI VFQ-25	●	●	●	●	●	●	●	●
Standard safety								
Prior / concomitant medications	●	●	●	●	●	●	●	●
Adverse events [d]	●	●	●	●	●	●	●	●
Hematology / chemistry	●							●
Urinalysis / UPCR	●							●
Pregnancy test – serum [e] (women of childbearing potential only)	●							
Pregnancy test – urine dipstick (women of childbearing potential only) [f]		●						●
Vital signs (body temperature, blood pressure, pulse)	●	●						●

BCVA = best corrected visual acuity; BL = baseline; ETDRS = Early Treatment Diabetic Retinopathy Study; UPCR = urine protein / creatinine ratio

a The intervals between Visits 6 to 9 are 8 weeks ±10 days.
The interval between Visit 9 and Visit 10 must be ≥ 56 days (8 weeks).

b Refraction to be done at each visit

c Also post injection

d 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).

e The test is to take place within 7 days before the first injection of the study medication

f The test is to be repeated as frequently as required

Section 9.2.1 Visit 1 - Screening

Urine dipstick pregnancy test no alternative to serum test in screening visit per Modification 9 (Section 15.1.1.9).

Old text:

Conduct

The following procedures will be performed at this visit:

…

- Pregnancy test in women of childbearing potential ~~(urine or serum test)~~

New text:

Conduct

The following procedures will be performed at this visit:

…

- Serum pregnancy test in women of childbearing potential

Section 9.2.2 Visit 2 (Day 1) - Baseline

Urine dipstick pregnancy test added for baseline visit per Modification 9 (Section 15.1.1.9)

Old text:

Conduct

The following procedures will be performed at this visit:

- Assessment of inclusion and exclusion criteria (see Sections 6.1 and 9 for details)

New text:

Conduct

The following procedures will be performed at this visit:

- Assessment of inclusion and exclusion criteria (see Sections 6.1 and 9 for details)
  - Including urine dip stick pregnancy test for women of childbearing potential

Section 9.2.4 Visit 11 (Week 52) - Final visit or early termination

Urine dipstick test required for pregnancy testing at this visit as per Modification 11 (Section 15.1.1.11).

Old text:

Conduct

…

- Pregnancy test in women of childbearing potential (urine ~~or serum~~ test)

New text:

Conduct

…

- Pregnancy test in women of childbearing potential (urine dipstick test)

Section 9.3.2 Medical/surgical and ophthalmic history

Addition of smoking history to the medical history per Modification 12 (Section 15.1.1.12).

Old text:

In addition, a complete ophthalmic history will be obtained to check the selection criteria as defined in Section 6.

New text:

In addition, a complete ophthalmic history will be obtained to check the selection criteria as defined in Section 6 and life style details including smoking history will be recorded.

Section 9.4 Efficacy

New Section 9.4.3 added per Modification 13 (Section 15.1.1.13)

Section 9.4.3 Efficacy variables

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

Section 9.4.1 National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ 25)

Requirement to document the name of the person assisting the subject in completing the NEI VFQ-25 questionnaire added per Modification 14 (Section 15.1.1.14).

Old text:

...

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.

New text:

...

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.

Section 9.4.2.6 Fundus photography (FP) and fluorescein angiography (FA)

Clarification for archiving as electronic archiving added per Modification 15 (Section 15.1.1.15).

Old text:

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

...

New text:

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

...

Section 9.6.1.5 Expected adverse events

Reference to summary of product characteristics replaced with reference to local label for information on AEs as per Modification 16 (Section 15.1.1.16).

Old text:

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

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

New text:

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

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

Section 9.6.2 Pregnancies

New paragraph on fertility added per Modification 17 (Section 15.1.1.17).

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

Section 9.6.3.1 Laboratory evaluations

Scheduling of serum and urine pregnancy test changed as per Modification 11 (Section 15.1.1.11) and addition of total and HDL cholesterol to the laboratory safety parameters per Modification 18 (Section 15.1.1.18).

Old text:

Laboratory evaluation will be conducted according to the schedule provided in Section 9.1. (beyond that schedule, pregnancy tests are to be done in women of childbearing potential as frequently as ~~demanded by local requirements~~.

Table 9-2: Laboratory safety parameters

Chemistry	Urinalysis	Hematology
Sodium	Glucose	Hemoglobin
Potassium	Protein	Hematocrit
Chloride	Specific Gravity	Red blood cell count
Calcium	Blood	Mean corpuscular volume (MCV)
Glucose	Ketones	Mean corpuscular hemoglobin concentration (MCHC)
HbA1c	Protein:Creatinine Ratio (UPCR)	Mean corpuscular hemoglobin (MCH)
Albumin		Leucocyte count
Total Protein, Serum	Pregnancy test for women of childbearing potential (urine or serum test is acceptable)	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		

New text:

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

Table 9-2: Laboratory safety parameters - amended

Chemistry	Urinalysis	Hematology
Sodium	Glucose	Hemoglobin
Potassium	Protein	Hematocrit
Chloride	Specific Gravity	Red blood cell count
Calcium	Blood	Mean corpuscular volume (MCV)
Glucose	Ketones	Mean corpuscular hemoglobin concentration (MCHC)
HbA1c	Protein:Creatinine Ratio (UPCR)	Mean corpuscular hemoglobin (MCH)
Albumin		Leucocyte count
Total Protein, Serum	Pregnancy test for women of childbearing potential (urine or serum see Table 9-1)	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

Section 10.3.2.1 Demography and baseline characteristics

Three analysis sets changed to two per Modification 19 (Section 15.1.1.19).

Old text:

Demographic variables and baseline characteristics will be summarized for ~~all three~~ analysis sets, 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).

New text:

Demographic variables and baseline characteristics will be summarized for both analysis sets, 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).

Section 10.3.2.3 Safety analyses

Summary of treatment groups removed per Modification 20 (Section 15.1.1.20).

Old text:

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.

New text:

Adverse events

Treatment-emergent AEs will be presented by MedDRA preferred term within primary system organ class (SOC). 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.

Section 13.4 Subject information and consent

Revised to align with sponsor standards per Modification 21 (Section 15.1.1.21).

Old text:

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 early-termination examinations as specified in the visit description described in Section 9.2.4 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. ~~For this, he/she needs to sign a corresponding declaration of objection; alternatively, the subject's oral objection may be documented in the subject's source data.~~ Each subject / legal representative or proxy 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 patient's note/file of the medical institution.

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

New text:

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 early-termination examinations as specified in the visit description described in Section 9.2.4 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 patient's note/file of the medical institution.

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

<u>If the subject is unable to read the informed consent form due to vision impairment, a family member, other legal representative of the subject, study nurse, or study physician may read the document to the subject and may assist the subject in signing the form. In this case, the name of that person should be documented.</u>

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.