Clinical Development

RFB002 (Ranibizumab; Lucentis®)

Protocol number (CRFB002ADE27 / NCT02257632) including Amendment 2

A randomized, single-blinded, multicenter, phase IV study to compare systemic VEGF protein dynamics following monthly intravitreal injections of 0.5 mg ranibizumab versus 2 mg aflibercept until study week 12 in patients with neovascular (wet) age-related macular degeneration

Acronym: TIDE AMD

Author(s): [redacted]

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Signature Pages for Amendment 2

Compound name / number: Ranibizumab (Lucentis®)/ RFB002

Protocol number: CRFB002ADE27

Approved by the following

Signatures of Novartis Personnel:

[redacted] signature date

[redacted] signature date

[redacted] signature date

Signature of Coordinating Investigator for Amendment 2

[redacted]

signature date

Signature Page for Investigator for Amendment 2

Compound name / number: Ranibizumab (Lucentis®)/ RFB002

Protocol number: CRFB002ADE27

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with the principles outlined in the Declaration of Helsinki. Note: Any deviations from this protocol require a formal amendment to be approved by the responsible ethics committee.

Investigator	signature	date
Center name / location:	institution (where applicable)	city

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List of abbreviations

ADA	American Diabetes Association
AE	adverse event
AMD	Age-related macular degeneration
ANCOVA	Analysis of covariance
AUC	Area under the curve
[redacted]	[redacted]
bpm	Beats per minute
BSL	Baseline
CF	Color fundus photography
CHMP	Committee for Medicinal Products for Human Use
CNV	Choroidal neovascularization
CRC	Central reading center
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
[redacted]	[redacted]
DME	Diabetic macular edema
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
[redacted]	[redacted]
EU	European Union
FA	Fluorescein angiography

FAS	Full analysis set
IB	Investigator's brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IRB	Institutional Review Board
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
PPS	Per-protocol Set
RPE	Retinal pigment epithelium
RS	Randomized Set
RVO	Retinal vein occlusion
SAE	serious adverse event
SCN	Screening
[redacted]	[redacted]
SmPC	Summary of product characteristics
VA	Visual acuity
VAP	Validation and Planning
VEGF	Vascular endothelial growth factor (-A) [redacted]
wAMD	Neovascular (wet) age-related macular degeneration
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
End of study visit	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
[redacted]	[redacted]
Fellow eye	The fellow eye is the non-study eye.
Investigational drug	The study drug whose properties are being tested in the study
Patient number	A number assigned to each patient who enrolls in the study; when combined with the center number, a unique identifier for each patient in the study is created.
Phase	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific study arm assignment
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug, combination of drugs and any control drugs including placebo
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal
Study eye	The study eye is the eye selected by the investigator at baseline (according to the protocol) to receive the study treatment
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Amendment 2

The protocol has been amended to correct two exclusion criteria in the protocol and to correct an error in table 7-1 .

At the time of the amendment, two patients have been randomized.

Changes to the protocol

- Exclusion criteria #4 was changed insofar that only patients with Type 1 or Type 2 diabetes mellitus with glycosylated hemoglobin (HbA1c) > 10% (> 86 mmol/mol) at screening are excluded from the study. Rationale: A large proportion of nAMD patients suffer from adult-onset diabetes and should have the possibility to be included in the study.
- Exclusion criteria #12: The clarification "…requiring treatment…" has been added. Rationale: Background for this exclusion criterion is that that the TIDE AMD study will investigate whether intravitreally injected anti-VEGF drugs have an effect on VEGF levels in the systemic circulation. An injection of the fellow eye should thus be avoided. Therefore not the medical condition of the fellow eye per se is excluded but the medical condition requiring treatment of the fellow eye with an anti-VEGF drug.
- Table 7-1: The ±1 day visit window of visit 3 was deleted. As written in chapter 7.9.1 the blood sampling at visit 3 should be performed 24 h ± 2 h after blood sampling at visit 2.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amendment require IRB/IEC and Health Authorities approval prior to implementation.

Amendment 1

The protocol has been amended to clarify and correct certain criteria and procedures in the protocol.

At the time of the amendment, no patients had been screened for inclusion.

Changes to the protocol

- The allocation of Exclusion criteria #19 was changed from "For fellow eye" to "For either eye". Rationale: The Inclusion criteria #4 states: "…newly diagnosed, untreated (…) CNV lesion…", which indicates that the study eye must not have had a previous treatment with any anti-angiogenic drug. To clarify this further within the exclusion criteria, the exclusion criteria #19 was changed as stated above.

- The description of Section 6.4 “Treatment assignment” was specified.
- A descriptive subgroup analyses to explore gender differences for primary results was added to Section 10.4.4 “Supportive analyses”.

The changes described in this amendment are non-substantial and require no Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities approval prior to implementation.

1 Background

Age-related macular degeneration (AMD) is the leading cause of blindness in individuals over the age of 55 years in developed countries (Coleman 2008). Most cases of severe visual loss in AMD are patients with wet (neovascular) AMD (wAMD), which is characterized by choroidal neovascularization (CNV) (Dhoot & Kaiser 2012). Increased expression of vascular endothelial growth factor A (VEGF-A) in the retinal pigment epithelium (RPE) is associated with the development of CNV lesions (Ozkiris 2010; Kovach 2012).

Intravitreal injection of a VEGF-A inhibitor is currently the standard treatment for neovascular AMD (Kovach 2012; Kaiser 2010).

VEGF inhibitors used in ophthalmology

i. Ranibizumab (Lucentis®) is a humanized recombinant monoclonal antibody fragment targeted against VEGF-A. Ranibizumab was approved for use in wAMD in 2007 in the European Union (EU) (Lucentis® EU Summary of Product Characteristics [SmPC]).

ii. Aflibercept (Eylea®) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG. Aflibercept binds and inhibits VEGF-A, VEGF-B, Placental growth factor (PlGF)-1 and -2 (Eylea® EU SmPC). Aflibercept was approved for use in wAMD in 2012 in the EU.

iii. Bevacizumab (Avastin®) is a full-length antibody raised against VEGF-A. Despite being only approved for the treatment of metastatic tumors (Avastin® EU SmPC), bevacizumab is used off-label by ophthalmologists for the treatment of neovascular pathologies in the eye.

In standard clinical practice, the treating ophthalmologist may change the drug or the treatment regimen if patients do not respond optimally to one of the previously mentioned anti-VEGF drugs or if intolerances or contraindications occur. Accordingly, patients may undergo one or several switches from one anti-VEGF drug to another during their therapy. The analysis of an american ophthalmologists' claim database revealed that 25% of wAMD patients were switched from one anti-VEGF drug to another during their first year of therapy (Ferreira 2013).

Systemic VEGF levels

Although the injection of VEGF inhibitors used to treat wAMD is performed intravitreally, there are several lines of evidence showing that a small portion of the drugs may pass to the systemic circulation and have systemic effects (see below).

This may be explained by the molecular biology underlying this process: Trials in adult mice showed that intravitreally administered full-length immunoglobulin G (IgG) was transported across the blood-retinal barrier into the systemic circulation. So called neonatal Fc receptors expressed in the blood-retina barrier are known to perform an Fc-dependent IgG transport and protect against their catabolism, resulting in their long serum half-life as compared with other proteins (Kim 2009; Yeung 2010). Both aflibercept and bevacizumab comprise an Fc fragment which suggests that an Fc-dependent transport of these anti-VEGF inhibitors to the systemic circulation takes place.

In contrast, ranibizumab represents an antibody Fab fragment only, which show greater retinal penetration and shorter systemic half-lifes than IgGs (Mordenti 1999). In addition, the absence of Fc eliminates the Fc-dependent transport across the blood-retina barrier, complement activation or cell-dependent cytotoxicity and thus results in a reduced systemic exposure than drugs comprising an Fc domain (Ferrara 2006; Raghavan & Bjorkman 2006). This was confirmed by studies in cancer which demonstrated that the systemic half-life of a Fab fragment is a few hours, whereas that of a full-length IgG is up to 3 weeks (Chong 2012; Reff 2002).

Under physiological conditions the VEGF pathway is essential for processes such as angiogenesis, vasodilation, endothelial cell integrity and for the glomerular filtration barrier (Chen & Cleck 2009). VEGF signaling plays a critical role in the homeostasis of the adult vascular system and VEGF is essential for cardiovascular repair and regeneration (Cruess 2013; Lee 2007). Inhibition of VEGF signaling can result in pathological consequences that include compromised wound healing and tissue repair, hypertension, arterial thromoembolic events, cardiac dysfunction, proteinuria or renal dysfunction (Chen & Cleck 2009). A sustained and significant reduction of systemic VEGF levels due to passage of intravitreally administered VEGF inhibitors may increase the risk for systemic side effects and thus should be avoided.

Only few studies report systemic VEGF level measurements following intravitreal anti-VEGF injections of ranibizumab and bevacizumab. It was shown that intravitreal injections of the full-length anti-VEGF-A antibody bevacizumab, but not of the Fab fragment ranibizumab significantly decrease systemic VEGF-A levels in wAMD patients. Following bevacizumab injections, systemic VEGF-A levels are reduced by -74% at day 28, -42% at month 3, -69% at month 12 and -78% at month 24 compared to baseline. In contrast, intravitreal ranibizumab injections only resulted in VEGF-A inhibition of -16% at day 28, -1% at month 3, -20% at month 12 and -28% at month 24 compared to baseline (Carneiro 2012; Chakravarthy 2012; Harding 2013; Zehetner 2013). A pooled analysis of two large clinical trials showed a significantly increased risk of any systemic SAE for treatment with bevacizumab compared to ranibizumab in patients with wAMD (Chakravarty 2013).

To date, only one study investigated the pharmacodynamic effect of aflibercept on systemic VEGF protein levels and reported a significant suppression of systemic VEGF levels after one intravitreal aflibercept injection of approx. -67% at day 7 and approx. -33% at day 28 compared to baseline. In contrast, wAMD patients receiving one intravitreal ranibizumab injection showed a change from baseline VEGF plasma levels of approx. + 6% at day 7 and approx. +12% at day 28 (Avery 2013).

Given that aflibercept features an Fc part, a similar transport mechanism for aflibercept over the blood-retina-border as for bevacizumab can be hypothesized. This assumption is in line with the aflibercept european public assessment report, which reports that almost 20% of intravitreally injected aflibercept passes to the systemic circulation. This was considered as an important potential risk in the aflibercept risk management plan (EMA CHMP assessment report on aflibercept, Procedure No. EMEA/H/C/002392/).

2 Study purpose

The purpose of the study is to compare the effect of intravitreal injections of ranibizumab and aflibercept on systemic VEGF protein levels in treatment naïve wAMD patients in a detailed time course.

The primary endpoint of this study is the area under the curve (AUC) of VEGF-A protein concentration in blood plasma between day 2 and study week 12. Both drugs will be administered as three monthly intravitreal injections.

In the second part of the study from study week 12 to week 24 all patients will receive three monthly ranibizumab injections and systemic VEGF-A protein levels will be compared between the two study groups. In addition, the study aims to explore whether systemic VEGF levels of patients switching from aflibercept to ranibizumab will adjust to levels comparable to baseline or to levels comparable as in patients treated with ranibizumab from baseline.

3 Objectives (and related endpoints)

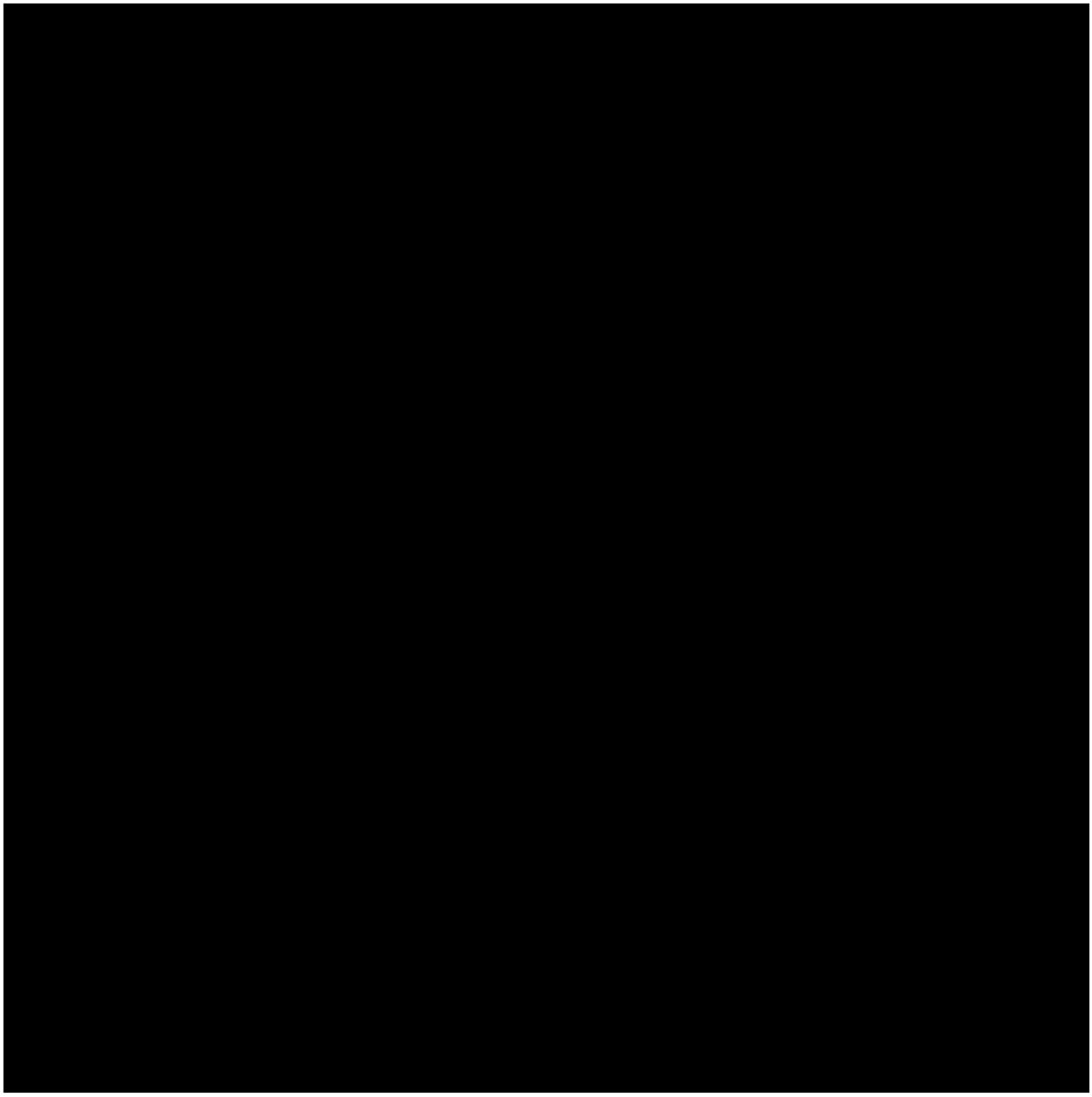
3.1 Primary objective(s)

To compare systemic VEGF-A protein levels following monthly intravitreal injections of 0.5 mg ranibizumab versus 2 mg aflibercept as measured by the area under the curve (AUC) from baseline to study week 12.

3.2 Secondary objective(s)

To compare systemic VEGF-A protein levels in patients switching from monthly 2 mg aflibercept injections to monthly 0.5 mg ranibizumab compared to patients treated with monthly 0.5 mg ranibizumab from baseline as measured by the AUC from study week 12 to week 24.

To explore whether systemic VEGF-A levels of patients switching from aflibercept to ranibizumab will adjust to levels comparable to baseline or to levels comparable as in patients treated from baseline with ranibizumab from study week 12, over time up to week 24.



4 Study design

This is a randomized, single-blinded, multicenter, phase IV study to compare systemic VEGF-A protein levels following monthly intravitreal injections of 0.5 mg ranibizumab versus 2 mg aflibercept until study week 12 in patients with wAMD. From week 12 on all patients will receive monthly intravitreal injections of 0.5 mg ranibizumab until study week 20 in order to compare systemic VEGF-A protein levels in patients switching from aflibercept to

ranibizumab injections with patients treated with ranibizumab only from study week 12 to week 24. A blinded central laboratory will evaluate systemic VEGF plasma levels.

Patients with wAMD will be randomized in a 1:1 ratio to one of the following treatment groups:

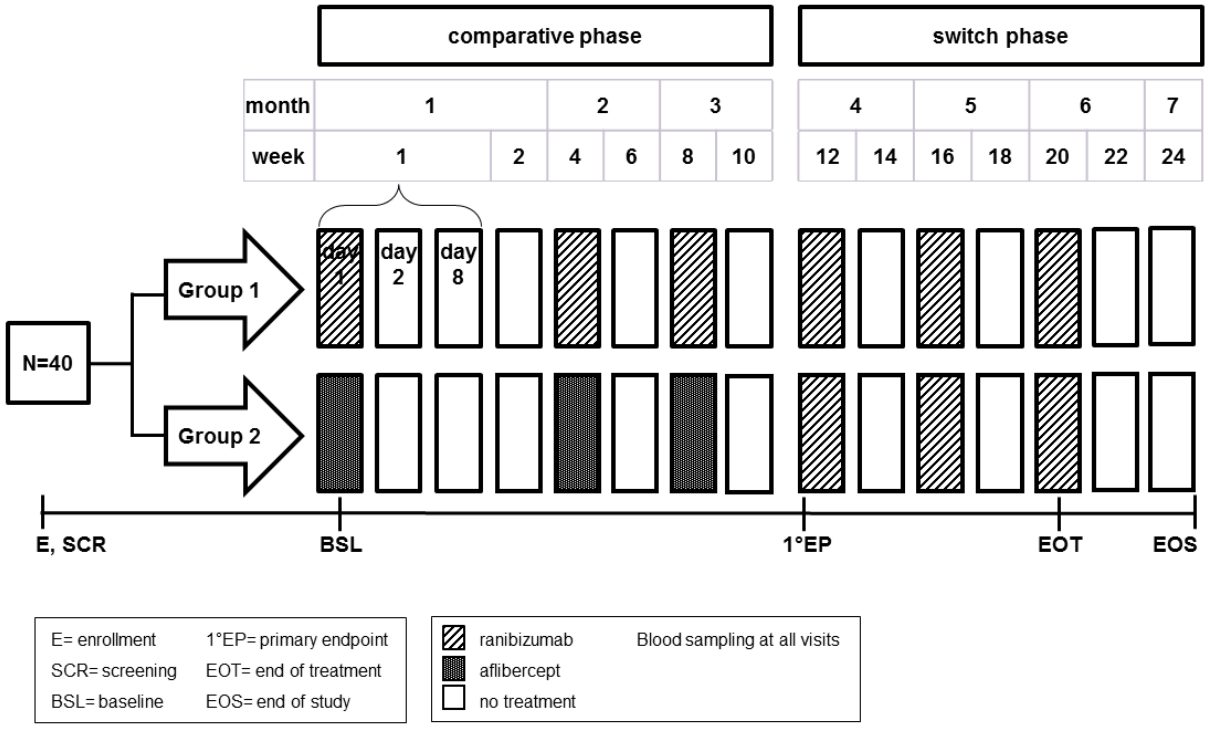
- Group 1: Six monthly intravitreal injections of 0.5 mg ranibizumab
- Group 2: Three monthly intravitreal injections of 2 mg aflibercept followed by three monthly intravitreal injections of 0.5 mg ranibizumab

The study requires 16 study visits during 24 weeks and the primary endpoint will assess data from baseline to study week 12.

At visit 1 (to occur between day -14 and day -1), after signing the informed consent, patients are enrolled into the study and procedures to allow assessment of the study eligibility criteria are performed. At the baseline visit on day 1 (visit 2), patients whose eligibility is confirmed will be randomized into one of the treatment arms (group 1 or group 2).

For an overview of the study design please see Figure 4-1 below:

Table 4-1 Study outline



5 Population

The study will include adult patients with active, newly diagnosed, untreated wAMD. A total of 40 patients (20 in each treatment arm) will be enrolled from approx. 7 centers across Germany. Patients will be treated in an outpatient setting.

5.1 Inclusion/exclusion criteria

The investigator must ensure that all patients who meet the following inclusion and do not fulfill any of the exclusion criteria are offered enrollment in the study.

5.1.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

Inclusion criteria for patient

1. Male or female patients, ≥ 18 years of age.
2. Written informed consent must be obtained before any study-related assessment is performed.

Inclusion criteria for study eye

3. Visual impairment predominantly due to neovascular AMD.
4. Active, newly diagnosed, untreated, angiographically documented, CNV lesion (i.e. leakage on fluorescein angiography plus intraretinal, subretinal or sub-RPE fluid on OCT) secondary to neovascular AMD in line with SmPC of ranibizumab (Lucentis®) and aflibercept (Eylea®).

5.1.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusion parameters can be applied by the investigator, in order that the study population will be representative of all eligible patients.

Exclusion criteria for systemic medical history and conditions

1. Any type of systemic disease or its treatment, including any medical condition (controlled or uncontrolled) that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk.
2. Stroke or myocardial infarction less than 3 months prior to screening.
3. Presence of uncontrolled systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg at the time of screening or baseline.
4. Type 1 or Type 2 diabetes mellitus according to ADA (2014) and/or WHO (2006) classifications (see Appendix 2, Table A2-2) with glycosylated hemoglobin (HbA1c) >

10% (> 86 mmol/mol) at screening. Diabetic patients should be on diet, exercise and/or pharmacological treatment for diabetes, which must have been stable for at least 3 months.

5. Known hypersensitivity to any of the study drugs or to drugs with similar chemical structures or to fluorescein or any other component of fluorescein formulation.

Exclusion criteria for ocular medical history and conditions

For either eye

6. Any active periocular or ocular infection or inflammation at the time of screening or baseline
7. Uncontrolled glaucoma (intraocular pressure [IOP] ≥30 mm Hg on medication or according to investigator's judgment) at the time of screening or baseline.
8. Neovascularization of the iris or neovascular glaucoma at the time of screening or baseline.

For study eye

9. Atrophy or fibrosis involving the center of the fovea at the time of screening or baseline.
10. Cataract (if causing significant visual impairment), planned cataract surgery during the study period, vitrectomy, aphakia, glaucoma surgery, severe vitreous hemorrhage, rhegmatogenous retinal detachment, proliferative retinopathy or choroidal neovascularization of any other cause than wAMD (e.g., ocular histoplasmosis, pathologic myopia) at the time of screening or baseline.
11. Irreversible structural damage within 0.5 disc diameter of the center of the macula (e.g., vitreomacular traction, epiretinal membrane, scar, laser burn, macular hole) at the time of screening or baseline that in the investigator's opinion could preclude visual function improvement with treatment.

For fellow eye

12. Retinal or choroidal neovascularization or macula edema requiring treatment of any cause at the time of screening or baseline or the anticipation of development of the above mentioned medical conditions requiring treatment within 3 months past screening or baseline.

Exclusion criteria for prior or current systemic medication

13. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives from screening, whichever is longer.
14. Use of any systemic anti-VEGF drugs (e.g., bevacizumab [Avastin®], ziv-aflibercept [Zaltrap®]).
15. Use of systemic or inhaled corticosteroids for at least 30 consecutive days within 3 months prior to screening.

16. Current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/hydroxychloroquine (Plaquenil®), tamoxifen, phenothiazines and ethambutol.

Exclusion criteria for prior or current ocular treatment

For study eye

17. Any intraocular procedure (including cataract surgery, Yttrium-Aluminum-Garnet capsulotomy) within 3 months prior to baseline or anticipated within the next 6 months following baseline.
18. Use of intravitreal or topical ocular corticosteroids administered for at least 30 consecutive days within 3 months prior to screening.

For either eye

19. History of treatment with any anti-angiogenic drugs (including any anti-VEGF agents, e.g., bevacizumab [Avastin®]).

Exclusion criteria for patient

20. Inability to comply with study or follow-up procedures.
21. Inability to give full informed consent.
22. Women
    - who are pregnant or breast feeding (pregnancy defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/ml))
    - who are menstruating and capable of becoming pregnant* and not practicing a medically approved method of contraception (Pearl Index <1**) during and up to at least 3 months after the end of treatment. A negative pregnancy test (serum) for all women and for girls entering menarche is required with sufficient lead time before inclusion

      *definition of post-menopausal: 12 months of natural (spontaneous) amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/m or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy

      **examples of particularly reliable methods with Pearl Index (PI) <1, according to guidelines of Deutsche Gesellschaft für Gynäkologie und Geburtshilfe:
      - hormonal oral contraception (Combination of estrogen and gestagen (, PI=0.1-0.9)
      - hormonal vaginal ring (combination of estrogen and gestagen, PI=0.65 uncorr.; 0.4 corr.)
      - hormonal transdermal patch (combination of estrogen and gestagen PI= 0.72 uncorr.; 0.9 corr.)
      - Estrogen-free ovulation inhibitors (containing desogestrel (PI=0.14)
      - Implanted hormones containing etonogestrel (PI=0-0.08)
      - Injectable 3-month depot progestins (PI=0.3-1.4; 0.88 corr.)
      - Intra-uterine progestine device (synthetic progestin containing IUDs, PI=0.16)

Oral contraceptives without estrogen (e.g. "mini-pills"), nonsynthetic progesterone only IUDs, female condoms, cervical shield, periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

23. Patients, who have already been randomized into this trial earlier must not be included a second time.
24. Study personnel or first degree relatives of investigator(s) must not be included in the study

5.2 Premature patient withdrawal

Patients must be withdrawn from the study for any of the following reasons:

- Withdrawal of informed consent
- Pregnancy
- Any prohibited treatment that leads to study withdrawal as listed in table 6-1.

Patients who discontinue study drug should NOT be considered withdrawn from the study. See Section 6.6.9 for the required assessments of these patients after study drug discontinuation.

Patients also should be withdrawn at any time if the investigator concludes that it would be in the patient's best interest for any reason. Protocol violations should not lead to patient withdrawal unless they indicate a significant risk to the patient's safety.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Completion CRF.

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study will not be replaced by newly enrolled patients.

6 Treatment

6.1 Patient numbering

Each patient in the study is uniquely identified by a 9 digit number which is a combination of his/her 4-digit center number and 5-digit subject number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 2, the third patient is assigned patient number 3). Once assigned to a patient, a patient number will not be reused for any other patient and number for that individual must not be changed, even if the patient is re-screened. If the patient fails to be randomized for any reason, the reason for not being randomized will be entered on the Screening Log.

6.2 Investigational drugs

Commercial available ranibizumab and aflibercept specially marked for clinical study only ("Zur klinischen Prüfung bestimmt") will be used and supplied in the study.

Ranibizumab and aflibercept must be stored according to the label instructions and must be kept in a secure locked facility.

Novartis will provide sufficient supplies of ranibizumab and aflibercept for treatment use to allow for completion of the study

6.2.1 Ranibizumab

The investigational drug in study group 1 from week 1 to week 24 and for study group 2 from week 12 to week 24 is 0.5 mg ranibizumab (Lucentis®).

Ranibizumab solution for injection in vials or prefilled syringes will be used. Ranibizumab is formulated as a sterile solution aseptically filled in a sterile glass vial or sterile prefilled syringe. Each vials or prefilled syringe contains ranibizumab in an aqueous solution (pH 5.5) with histidine, trehalose, and polysorbate 20. Each vial or prefilled syringe is for single use only. Each vials or prefilled syringe will be labeled with the appropriate information.

Each patient will either be treated only with ranibizumab in vials or only treated with ranibizumab in prefilled syringes throughout the entire study.

6.2.2 Aflibercept

Investigational treatment drug in study group 2 from week 1 to week 8 is 2 mg aflibercept (Eylea®).

Aflibercept solution for injection will be supplied in commercially available packaging. Aflibercept is formulated as a sterile solution aseptically filled in a sterile glass vial. Each vial

contains aflibercept in an aqueous solution with monosodium phosphate, disodium phosphate, sodium chloride, sucrose and polysorbate 20. The vials are suitable for single use only. Each vial will be labeled with the appropriate information.

6.3 Treatment arms

Patients will be assigned to one of the following two treatment groups (=arms) in a ratio of 1:1:

- Group 1: Six monthly intravitreal injections of 0.5 mg ranibizumab
- Group 2: Three monthly intravitreal injections of 2 mg aflibercept followed by three monthly intravitreal injections of 0.5 mg ranibizumab

6.4 Treatment assignment

At visit 2 (baseline) all patients who meet the inclusion and do not fulfill any of the exclusion criteria will be given the card with the lowest available randomization number. This number will be assigned to the patient by the physician, who will enter the patient randomization number on the CRF. The physician will then look up the corresponding treatment on the allocation card (containing randomization numbers and corresponding treatment arm) and administer the study treatment accordingly.

The patient randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and evaluating staff: A patient randomization list will be produced by or under the responsibility of Novartis using a validated system.

6.5 Treatment blinding

Given that the primary endpoint variable will be assessed by a blinded central laboratory, it is considered to be adequate that the injecting physician will not be blinded to treatment. The injecting physician has no influence on treatment regimen or primary or secondary endpoint assessments. The study will therefore be performed as a single-blinded study. Only patients, [redacted], reading center staff, laboratory staff and data analysts will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by blinded staff involved in the study.

The study center staff or the physician must be vigilant not to unblind the patient, [redacted] Novartis personnel, the reading center or central laboratory to the treatment. The physician is responsible for keeping the treatment allocation cards in a secure locked place where [redacted] has access to.

Unblinding will only occur at the conclusion of the study.

6.6 Treating the patient

6.6.1 Dispensing the study drug

Ranibizumab and aflibercept medication will be supplied as commercially available Lucentis® or Eylea® with an additional label stating that it is being used in a clinical study.

6.6.2 Instructions for use of study drug

Intravitreal injections will be administered as described in the SmPC for Lucentis® and Eylea®.

After eligibility confirmation at baseline (day 1), patients will receive treatment according to their assignment into one of the two treatment groups (=arms) (see Sections 6.6.2.1 and 6.6.2.2).

The prefilled syringe or the vial will be taken from the package and treatment will be performed. After that the prefilled syringe (with needle removed) or empty vial will be put back in the commercial package and should be marked with patient number by the physician to make drug accountability possible. It will be stored at a secured locked and different location than unused packages and commercial (non-study) packages to avoid mix-up.

All dosages prescribed and dispensed to the patient must be recorded on the Drug Administration Record CRF.

The storage conditions for study drug will be described on the medication label.

6.6.2.1 Treatment group 1

Beginning at baseline, patients randomized to the study group 1 will receive monthly intravitreal injections of 0.5 mg ranibizumab (visit 2, 6, 8, 10, 12 and 14)

The interval between two intravitral injections should not be shorter than 28 days.

6.6.2.2 Treatment group 2

Patients randomized to the study group 2 will receive three initial monthly injections of 2 mg aflibercept (visit 2, 6 and 8). This is followed by three monthly intravitreal injections of 0.5 mg ranibizumab (visit 10, 12 and 14).

The interval between two intravitreal injections should not be shorter than 28 days.

6.6.2.3 Treatment of the fellow eye

Patients, who develop an indication at the fellow eye that, in the investigator's opinion, qualifies for and requires treatment, may be treated at the investigator's discretion according to the standard of care. Administration of treatment to the fellow eye must be recorded on the Concomitant medication/Significant non-drug therapies page of the CRF (dose, timing and type of treatment).

Anti-VEGF treatment of the fellow eye leads to study withdrawal.

6.6.3 Study drug supply and resupply, storage, and tracking

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only physician and designated assistants have access. Upon receipt, all study drugs should be stored according to the instructions specified on the drug labels.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial.

At the conclusion of the study and as appropriate during the course of the study, the investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.6.4 Study drug compliance and accountability

6.6.4.1 Study drug compliance

Dosing frequency and compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.6.4.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in the Drug Accountability Log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Investigators will be asked to keep all unused study drug and packaging until monitoring of drug accountability.

6.6.5 Disposal and destruction

After drug accounting has been checked by monitor, at study close-out and, as appropriate during the course of the study, all used and unused study treatment, packaging, drug labels, and drug accounting forms will be returned to Novartis for destruction.

6.6.6 Permitted study drug dose adjustments and interruptions

Dose adjustments, i.e., adjustments of the injection volume of ranibizumab or aflibercept dose solution, are not permitted.

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

- [redacted]
- An IOP of ≥30 mm Hg,
- An untreated retinal tear is diagnosed,

- A subretinal hemorrhage involving the center of the fovea, or, if the size of the hemorrhage is ≥50%, of the total lesion area,
- A performed or planned intraocular surgery within the previous or next 28 days.

All interruptions must be recorded on the Drug Administration Record CRF.

6.6.7 Rescue medication

Rescue medication is not forseen in this study.

6.6.8 Other concomitant treatment

Use of treatments, as displayed in Table 6-1 is NOT allowed after screening. In addition, there are certain wash-out periods to be respected as outlined in the list of exclusion criteria.

Table 6-1 Prohibited treatment

Medication	Action to be taken
Systemic or ocular (fellow eye) anti-VEGF drugs	Study withdrawal
Intra- or periocular corticosteroids (including sub-Tenon but excluding topical formulations) – study eye	Study withdrawal
Medications known to be toxic to the lens, retina or optic nerve including deferoxamine, chloroquine/ hydroxychloroquine (Plaquenil®), tamoxifen, phenothiazines, and ethambutol	To be recorded in the CRF
Other investigational drugs and investigational interventions of any type	To be recorded in the CRF

The investigator should instruct the patient to notify the study site about any new medications he/she takes after enrollment into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the CRF.

Protocol specific medications (e.g., dilating drops, fluorescein dyes) and pre- and post-injection medications (e.g., topical anesthetics) used by a patient during the study are not considered concomitant medications.

Patients who are prematurely withdrawn from the study should be scheduled for visit 16 as soon as possible, at which time all of the assessments listed for the final visit will be performed.

6.6.9 Study drug discontinuation

Patients can discontinue study treatment because of the appearance of a new health condition suspected to require appropriate, unacceptable AEs, refusal to continue treatment, or at the investigator's discretion based on his or her clinical judgment.

Study drug must be discontinued for a given patient if the investigator determines that continuing it would result in a significant safety risk for that patient. The following circumstances **require** study drug discontinuation:

- Emergence of the following adverse events:
  - macular hole (stage 3 or 4) in the study eye
  - rhegmatogenous retinal detachment in the study eye
  - transient ischemic attack (TIA) or a stroke during the study
- Any other protocol deviation that results in a significant risk to the patient's safety.

Patients who discontinue study treatment should not be considered withdrawn from the study and the investigator should encourage the patient to continue in the study and to return for the remaining visits as described in Table 7-1.

In addition, all the criteria listed under 5.2 for premature patient withdrawal will automatically lead to study drug discontinuation. In addition to these requirements for study drug discontinuation, the investigator should discontinue study drug for a given patient if, on balance, he thinks that continuation would be detrimental to the patient's well-being.

6.6.10 Emergency unblinding of treatment assignment

Emergency code break cards are not applicable since the investigator is unblinded.

6.6.11 Study completion and post-study treatment

The study will be considered completed for an individual patient when he/she completes study visit 16.

Patients who already have entered the Screening Period should not enter the Treatment Period once the planned number of patients has been found eligible to commence treatment in the study.

The study can be terminated for reasons stipulated in the study contract. Should this be necessary, the patients should be contacted and scheduled for their end of study assessments as described in Section 7. Novartis will be responsible for informing IRBs and/or IECs of the early termination of the study.

The investigator also must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

7 Visit schedule and assessments

Table 7-1 lists all of the patient`s assessments and indicates with an "X" the visits when they are performed.

A planned study visit schedule will be established at the time of baseline visit (day 1) for all patients. Study assessments for patients will be performed at screening visit, baseline (day 1), day 2, day 8 (± 1 day to allow for flexibility in scheduling) and as of day 15 through to day 169 at biweekly visits (defined as every 14 days calculated from baseline; ± 4 days to allow for flexibility in scheduling).

Should a deviation from the study visit schedule occur, all efforts should be made to return to the planned visit schedule taking into consideration the restrictions on the minimum treatment interval between ranibizumab or aflibercept treatments, which should be ≥ 28 days.

Study site personnel will contact each patient via telephone 2 days (± 1 day) after each study treatment to elicit reports on AEs. If in consequence clinical assessment is required, patients will be scheduled to return to the site for an unscheduled visit and all findings will be recorded on the unscheduled visit assessment CRF. Patients will be further instructed to contact their investigator at any time should they have health-related concerns.

Patients who are prematurely withdrawn from the study for any reason should be scheduled for visit 16 as soon as possible, at which time all of the assessments listed for the final visit will be performed.

Patients who discontinue study drug before completing the study should be encouraged to return for the remaining visits as described in Table 7-1. If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the primary reason. At a minimum, they will be contacted for safety evaluations during the 30 days following the last dose of study drug, including final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the patient record.

All data obtained from the assessments listed in Table 7-1 and described in detail in the subsections below must be supported in the patient's source documentation.

Table 7-1 Assessment schedule for patients

Period		SCN	BSL														EOS
Visit number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Study month (relative to Day 1)			1				2		3		4		5		6		7
Days (relative to Day 1)		-14 to -1	1	2	8	15	29	43	57	71	85	99	113	127	141	155	169
Visit window (days)					± 1	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4	± 4
Information & Informed consent		X															
Inclusion/Exclusion criteria		X	X														
Diagnosis		X															
Demographics		X															
Medical history		X															
Prior/concomitant medication		X	X				X		X		X		X		X		X
Randomization			X														
Blood sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																	
Color Fundus Photography		X [a]	X								X						X [a]
Fluorescein Angiography		X [a]															X [a]
Ophthalmoscopy (Fundus)		X [a]	X				X		X		X		X		X		X [a]
Anterior Biomicroscopy (Slit lamp)		X [a]	X				X		X		X		X		X		X [a]
Tonometry		X [a]	X [b]				X [b]		X [b]		X [b]		X [b]		X [b]		X [a]
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	Height		X														
	Weight		X								X						X
	Pulse rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test [c]		X															X

Urine sample			X								X					X
Treatment: Group 1	Ranibizumab		X[d]				X[d]		X[d]		X[d]		X[d]		X[d]		
Treatment Group 2	Aflibercept		X[d]				X[d]		X[d]								
	Ranibizumab										X[d]		X[d]		X[d]		

a= Assessment to be performed also on fellow eye

b= Tonometry has to be performed before and after drug administration.

c=For women of child-bearing potential, serum pregnancy test at screening, urine pregnancy test at the end of study

d= Including post-injection assessment after intravitreal injection according to investigator's judgment, such as vision check, optic nerve head perfusion

7.1 Information to be collected on screening failures

Only demography data and the reason for failing (screening failure log) are collected for those patients who fail to enter the study phase. Blood samples of screening failures will be discarded.
Potential adverse events and hospitalizations which may have occurred from time of signing informed consent/written assent until screening failure time should be documented in the patient medical records. Reporting of potential SAE during this time period should be followed as described in Section 8.2.

7.2 Demographics/other baseline characteristics

The following information will be collected/documented at screening (visit 1) and/or baseline (visit 2):

- Year of birth
- Age
- Sex
- Race
- Past medical history and current medical conditions
- Prior/ concomitant medications
- Vital signs
- Study eye
- CNV lesion type and location
- [redacted]
- Area of CNV lesion and CNV leakage on FA, presence of hemorrhage on CF
- Infection status by using slit lamp examination
- Intraocular pressure
- [redacted]
- Pregnancy testing
- Blood sampling for assessment of systemic VEGF levels, [redacted]
- [redacted]
- Smoking status

7.3 Treatment exposure and compliance

Treatment exposure will be assessed for the study eye. Information regarding study treatment administration or any protocol deviations of treatment administration in the study eye will be collected on the Drug Administration Record CRF.

Any deviations from the protocol in use of prohibited medications (e.g. anti-VEGF) during the study will be collected on the Concomitant medications/Significant non-drug therapies page of the CRF.

7.4 Efficacy

The assessment for the primary endpoint, systemic VEGF-A plasma protein concentration, is described in Section 7.9.

Efficacy assessments will include both functional and anatomical evaluations. The methods of evaluation and the parameter to be assessed are listed below.

[redacted]

These patient's assessments are performed according to the schedule in Table 7-1. All efficacy assessments are to be done on the patient`s study eye and recorded in the CRF.

[redacted]

7.4.3 Color Fundus Photography and Fluorescein Angiography

Patients must be assessed using the same camera throughout the course of the study.

Fluorescein angiography (FA) is to be done in conjunction with color fundus photography (CF) at screening/visit 1 and visit 16 for both eyes, and color fundus photography of the study eye only at visit 2 and 10. Investigators will use digital fluorescein angiograms to determine the presence or absence of CNV secondary to AMD.

FA and CF image files will be exported, labeled, saved to DVD and sent to the central CRC following the instructions in the clinical site instruction manual.

A copy of the photographs and angiograms will be retained with the source documents.

All CRC staff performing the assessments of FA and CF images will be blinded to the identity of the treatment.

Novartis requires certification for FA evaluation. An operations manual and training materials for the certification will be provided by the central reading center. Certification will occur prior to any evaluation of study patients.

7.5 Safety

7.5.1 Adverse events

For details on adverse event collection and reporting, refer to Section 8.

7.5.2 Physical examination

No physical examination will be performed.

7.5.3 Vital signs

The results will be recorded in the Vital Signs CRF. Clinically notable vital signs are defined in Appendix 2, Table A2-1.

At visits when treatment is administered, vital signs will be measured prior to the intravitreal injection.

7.5.3.1 Height and weight

Height in centimeters (cm) will be measured at visit 2.

Body weight (in indoor clothing, but without shoes) will be measured at visits 2, 10 and 16.

7.5.3.2 Pulse rate

At each visit, the pulse rate (beats per minute-bpm) will be measured in the sitting position for 30 seconds just prior to the blood pressure measurements.

7.5.3.3 Blood pressure

At each study visit, after the patient has been sitting for at least five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressures will be measured three times using an automatic blood pressure monitor and appropriate size cuff.

The repeat sitting measurements will be made with approximately 3 minute resting intervals in between and the mean of these three blood pressure measurements will be used as the average sitting blood pressure for that visit (mmHg) and will be recorded in the patient's source documents and CRF.

At the first study visit, sitting blood pressure should be measured in both arms and the arm in which the highest sitting diastolic blood pressure is found will be the arm used for all subsequent readings throughout the study and should be documented in the source documents.

7.5.4 Laboratory evaluations

No specific laboratory evaluations for safety assessment will be performed. Laboratory evaluations for serum pregnancy testing, pharmacodynamics [redacted] are described in Sections 7.5.5, 7.9 and 7.11, respectively.

7.5.5 Pregnancy test and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test at screening (visit 1) and a urine pregnancy test at the end of study (visit 16). Results will be recorded in the respective CRF. A central laboratory will be used for analysis of the serum.

7.5.6 Eye-specific safety monitoring

The standard ophthalmic examinations include slit lamp examination, anterior chamber examination, direct and indirect ophthalmoscopy of the macular and peripheral retina, and tonometry. They will be performed as indicated in the assessment schedule (Table 7-1). Slit lamp and fundus examinations will be performed prior to treatment with ranibizumab or aflibercept.

The test results will be recorded in the source documents and clinically significant abnormalities will be recorded on the medical/ocular history page (if occurring before BSL) and if occurring after the first injection with investigational drug, on adverse event page of the CRF.

7.5.6.1 Anterior segment biomicroscopy (slit lamp examination)

Prior to administration of treatment, the anterior segment's structures of the study eye will be carefully examined. If needed, an additional examination will be performed after application of any study medication. Fellow eye will be examined at screening (visit 1) and visit 16 and during the study on discretion of the investigator.

7.5.6.2 Ophthalmoscopy

At the screening (visit 1) and visit 16 the posterior segment of both eyes will be examined by the investigator on dilated pupil using adequate ophthalmoscopy apparatus in order to confirm the clinical findings compatible with CNV secondary to wAMD as inclusion criteria's assessments. Also a careful examination of the peripheral retina must be conducted to ensure that the intravitreal injection can safely be performed (i.e. iatrogenic retinal detachment, should not be receive intravitreal injections).

At the indicated visits from baseline (visit 2) on, assessment of the posterior of the study eye will be performed and recorded by the investigator and an additional examination if needed will be performed after the application of the study medication. If the patient experiences blurred vision and light flashes at any time, the investigator should perform the indirect ophthalmoscopy examination in order to detect any AEs and apply the appropriate treatment. In case of uncertainty regarding the clinical findings at the macular area with ophthalmoscopy, a complementary examination using a suitable lens through slit lamp apparatus can be done for the study eye by the investigator.

7.5.6.3 Intraocular pressure (IOP)

Both eyes IOP will be measured at screening (visit 1) and visit 16. Pre-dose IOP in the study eye will be assessed by the investigator or trained technician at every scheduled visit as from

visit 2 (day 1) and post-dose IOP will be assessed 15 to 60 minutes after injection in the study eye. The values will be recorded in mmHg and will be entered into the CRF.

In case intraocular pressure is ≥25 mmHg in the study eye, and if not transient, for any reason and at any time during the study period, treatment and closer monitoring of IOP should be performed by the investigator in order to achieve similar values to the baseline measurement. In this case, intravitreal procedure is not recommended unless normalization of the IOP has been achieved. The investigator should treat appropriately the increased IOP in order to allow the patient to continue in the study. In addition, at the discretion of the investigator and/or according to the local requirements/practices, monitoring of optic nerve head perfusion may be appropriate within 30 minutes after injection. Results of these procedures will be recorded in the source documents. Only if the findings constitute an AE they have to be recorded in the AE CRF.

7.6 Tolerability/acceptability

Tolerability of the treatment will be assessed through AE reporting in this study.

7.7 Resource utilization

Data for Healthcare Resource Allocation will not be collected for this study

7.8 Health-related Quality of Life

Halth-related Quality of Life will not be collected for this study

7.9 Pharmacokinetics/pharmacodynamics

7.9.1 Pharmacodynamics

A central laboratory will be used for analysis of systemic VEGF (-A[redacted]) plasma levels of all specimens collected. If an intravitreal injection is administered at the same visit, blood sampling must be conducted prior to administration of the drug. Blood samples will be taken as shown in assessment schedule in Table 7-1. Blood sampling at visit 3 should be performed 24 h ± 2 h after blood sampling at visit 2. Details on the collections, labelling, storage and shipment of samples are provided to investigators in the laboratory manual.

All central laboratory staff performing the assessments of systemic VEGF plasma protein levels will be blinded to the identity of the treatment.

7.10 Pharmacogenetics/pharmacogenomics

Not applicable.

8 Safety monitoring

8.1 Adverse events

8.1.1 Adverse event definition and reporting

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after first intake of study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during any period of the study.

Medical conditions/diseases present before first administration of study drug are only considered adverse events if they worsen after study start. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, require dose reduction or temporary or permanent study drug discontinuation or require therapy.

All adverse events with a date of onset up to 30 days following the last dose of study drug must be reported.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its relationship to the ocular injection (suspected/not suspected)
4. its duration (start and end dates or if continuing at final exam)
5. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.
Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, seriousness, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

8.1.2 Laboratory test abnormalities

Laboratory abnormalities that constitute an Adverse Event in their own right (are considered clinically significant, induce clinical signs or symptoms, require dose reduction or temporary or permanent study drug discontinuation or require concomitant therapy), should be recorded

on the Adverse Event CRF page. Whenever possible, a diagnosis, rather than a symptom should be provided. Laboratory abnormalities that meet the criteria for an Adverse Event should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events.

A grade 3 or 4 event or laboratory abnormality (severe) as per CTCAE (if applicable) does not automatically indicate an SAE unless it meets the definition of serious as defined below and/or as per investigator´s discretion. If a lab event satisfies the regulatory definition of "Serious", such an event must be reported to Novartis within 24 hours of learning of its occurrence. Any laboratory SAEs experienced 30 days after completion of the study period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

8.2 Serious adverse events

8.2.1 Serious adverse event definition, treatment and follow-up

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; SAEs in contrast to AEs need to be reported from informed consent on, see Section 8.2.2.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure or Summary of product characteristics, respectively, or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.2.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. For patients who discontinue study medication, SAEs still need to be reported until the end of study, regardless of their suspected relationship to study medication.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the German Novartis Clinical Safety & Epidemiology Department. The telephone and telefax number of the contact persons in the German department of Clinical Safety and Epidemiology, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

All serious AEs occurring during the follow-up will be entered in the Adverse Events CRF pages. In addition, an SAE Report Form should be completed. Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Clinical Safety & Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancy reporting

To ensure patient safety, each pregnancy in a patient on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Instances of pregnancies and positive pregnancy tests should be collected for all patients who have conceived after receiving study medication. Pregnancies that are noted prior to administration of study medication but after signing informed consent may require reporting if they are considered to be associated to the conduct of the study by the investigator.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the German Novartis Clinical Safety & Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8.4 Reporting of adverse events and pregnancies after the last dose of study drug taken

All AEs, SAEs, and pregnancies which occurred within 30 days after intake of last dose of study drug should be reported. After this 30-day period, only SAEs, and pregnancies should be reported until the last visit.

8.5 Data Monitoring Board

Not applicable.

9 Data review and database management

9.1 Site monitoring

Before study initiation, at a site initiation visit, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

9.2 Data collection

Designated investigator staff must enter the information required by the protocol onto the Novartis CRFs that are printed on 3-part, non-carbon-required paper. Field monitors will review the CRFs for completeness and accuracy and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to Data Management by field monitors, one copy being retained at the investigational site. Once the CRFs are received by Data Management, their receipt is recorded and they are reviewed prior to data entry.

9.3 Database management and quality control

Data from the CRFs are entered into the study database by Contract Research Organization staff following their own internal standard operating procedures that have been reviewed and approved by Novartis.

Subsequently, the entered data are systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Errors are corrected by Data Management personnel as preliminary corrections. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution. The signed original and resolved Data Query Forms are kept with the CRFs at the investigator site, and a copy is sent to Novartis so the resolutions can be entered into the database. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Fluorescein angiograms, color fundus photographs and [redacted] will be processed centrally by the reading center and the results will be sent electronically to Novartis (or a designated CRO).

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Trial Statistician and Statistical Reporting and the Clinical Trial Leader.

10 Data analysis

The data will be analyzed by Novartis and/or by the designated CRO. Any data analysis carried out independently by the investigator(s) should be submitted to Novartis before publication or presentation

It is planned that the data from all centers that participate in this protocol will be used, so that an adequate number of patients will be available for analysis.

Data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetic and pharmacodynamic measurements, [redacted].

10.1 Populations for analysis

The **Randomized Set (RS)** will consist of all patients who were randomized to one of the treatment arms.

The **Full Analysis Set (FAS)** will consist of all patients as randomized who receive at least one application of study treatment and have at least one post-baseline assessment of the primary efficacy variable (plasma VEGF-A concentration). Following the intent-to-treat principle, patients will be analyzed according to the treatment they were assigned to at randomization. No data will be excluded from the FAS analyses because of protocol deviations.

The **Safety Set** will consist of all patients that received at least one application of study treatment and had at least one post-baseline safety assessment. Patients will be analyzed according to treatment received. Of note, the statement that a patient had no adverse events also constitutes a safety assessment.

The **Per-Protocol Set (PPS)** will consist of all patients who did not show major deviations from the protocol procedures that might have an impact on the study outcome. Criteria that are assumed to have such an impact will be defined in the data validation document (VAP) and in the Blind Review Protocol before unblinding.

The primary analysis will be performed for both, the FAS and the PPS. The PPS is regarded as primary. FAS will be interpreted in terms of sensitivity analysis.

10.2 Patient demographics/other baseline characteristics

Descriptive statistics will be provided for patient demographics and all baseline characteristics (including the baseline values of the efficacy endpoints).

Relevant medical history (ocular and non-ocular) and current medical conditions will be tabulated by system organ class and preferred term of the MedDRA dictionary. Separate tables will be provided for ocular (in study eye and fellow eye) and non-ocular histories and conditions. Other relevant baseline information will be listed and summarized as appropriate with descriptive statistics.

Analyses on patient demographics will be based on the RS.

10.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

10.3.1 Investigational Treatment

Descriptive statistics will be provided for exposure to study treatment using the Safety Set. The number of ranibizumab and aflibercept injections will be presented by treatment arm in frequency tables by visit and cumulatively.

10.3.2 Concomitant therapies

The number and percentage of patients taking concomitant therapies will be summarized by preferred term according to the WHO Drug Reference List dictionary using the Safety Set.

Summaries will be presented over two time periods: therapies received prior to the start of study treatment and therapies received after the start of study treatment.

10.4 Analysis of the primary objective(s)

10.4.1 Variable

The primary variable is the area under the curve (AUC) of VEGF-A protein concentration in plasma measured between day 2 and study week 12. The AUC will be standardized (=divided) by the individual follow-up time and will be calculated by the trapezoidal rule.

10.4.2 Statistical hypothesis, model, and method of analysis

The null hypothesis states no difference in systemic VEGF-A levels between ranibizumab and aflibercept monthly therapy, measured by an AUC. The level of significance is 5% two-sided.

The primary analysis will be performed by an analysis of covariance (ANCOVA) model with the factors center and treatment taking into account the baseline systemic VEGF-A level as a covariate. Raw- as well as adjusted (LS-) means with corresponding 95% confidence intervals and p-values will be calculated as point estimates for the treatment contrasts.

Multiplicity issues are not applicable because there is only one primary comparison. As there is very little knowledge about the distribution of systemic VEGF-A levels and especially on the variability, a blinded pooled interim analysis of the Variance of VEGF-A levels is planned to possibly adapt the planned sample size only, as described below.

10.4.3 Handling of missing values/censoring/discontinuations

The primary endpoint measure is calculated as an AUC and any patient not providing any post baseline value into the analysis is defined not to be included in the FAS. Consequently, there is no need to impute for missing values. In case there are only one or two out of the eight values for a patient, the area change can still be calculated preventing any dropouts other than those with no post baseline measurements.

10.4.4 Supportive analyses

The primary analysis will be repeated for the FAS to evaluate robustness of the results of the primary analysis. In case of relevant deviations from the normal distribution, non parametric analyses may be taken into account. Furthermore, careful examination of the distribution of the VEGF-levels will be prepared for the blind review meeting. If outliers or other properties of the distribution make it seem more appropriate, a log-transformation of the data or multiplicatory models will be taken into account, even for primary analysis if this is deemed reasonable. Also an analysis using relative changes instead of absolute differences in VEGF levels may be considered in case this is deemed reasonable during blind review.

Furthermore, descriptive subgroup analyses will be prepared to explore gender differences for primary results.

10.5 Analysis of secondary objectives

To compare systemic VEGF-A protein levels in patients switching from monthly 2 mg aflibercept injections to monthly 0.5 mg ranibizumab compared to patients treated with monthly 0.5 mg ranibizumab from baseline. The analysis will be performed following the same methods as for the primary analysis taking into account the levels measured between week 12 and 24.

To explore whether systemic VEGF-A levels of patients switching from aflibercept to ranibizumab will adjust to levels comparable to baseline or to levels comparable as in patients treated from baseline with ranibizumab from study week 12, over time up to week 24

10.5.2 Safety

Safety analyses will be based on adverse events, vital signs, laboratory evaluations, ophthalmic examinations and IOP.

All safety analyses will be performed using the Safety Set.

Adverse Events

AEs will be deemed treatment emergent if the onset date is on or after the date of first study treatment. AEs recorded prior to the start of study treatment will be listed separately. Only treatment-emergent AEs will be summarized.

AEs will be summarized by presenting for each treatment arm the number and percentage of patients having any AE, having an eye-related AEs, having an AE in each primary system organ class and having each individual AEs based on the preferred term. Patients who experienced multiple AEs for a preferred term will be counted once, similarly for patients with multiple AEs per system organ class.

All other information collected (e.g., severity or relationship to study treatment) will be tabulated and listed as appropriate. Summary tables will also be presented for the subset of AEs suspected to be treatment related.

Vital signs and IOP measurements will be presented descriptively (absolute values and change from baseline). Results from ophthalmic examinations will be listed.

Deaths, SAEs, and AEs leading to discontinuation of study treatment will be listed separately and, if appropriate, summarized by primary system organ class and preferred term.

For a given treatment period in the crossover design of treatment arm 2, the only AEs that will be counted for that treatment will be treatment-emergent events. These events are those that started after the start of that treatment period, or were present prior to the start of the treatment period but increased in severity, changed from being not suspected to being suspected to be due to study drug, or developed into an SAE after the start of the treatment period

10.5.3 Tolerability

Tolerability will not be assessed separately and will be included in the AE reporting.

10.5.4 Pharmacokinetics/ pharmacodynamics

10.5.4.1 Pharmacodynamics

Please also refer to Section 10.4.1 for the analysis of the primary objective variable and to Section 10.5 for the analysis of the secondary objective variable.

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

10.6 Interim analysis

There is only very little knowledge about the distribution of systemic VEGF-A levels and especially on the variability. Thus, as an over- or underestimation of the variance and consequently of the standardized effect size might jeopardize the adequacy of the planned sample size, a blinded pooled interim evaluation of the variance of VEGF-A levels is planned when 20 patients (10 in each treatment arm) completed study week 12 to possibly adapt the planned sample size only. This analysis is intended to adjust the sample size if necessary while limiting the interventions (e.g. blood sampling) to as little patients as necessary. No further treatment unblinding and especially no interim efficacy analysis will be performed. This interim analysis will not use any unblinded data, therefore no adjustment of the type-1-error levels is required.

10.7 Sample size calculation

In the past, measuring systemic VEGF protein levels was performed differently in the literature available. While some authors used blood plasma (Avery 2013; Carneiro 2012; Zehetner 2013), others used blood serum (Chakravarthy 2012). In addition, individual systemic VEGF levels seem to be very variable, depending e.g. on the state of health, hormone levels or menstrual cycle.

To date, only one study investigated the pharmacodynamic effect of aflibercept on systemic VEGF protein levels (Avery 2013). Given that aflibercept features an Fc part, a similar transport mechanism for aflibercept over the blood-retina-border as for bevacizumab can be hypothesized.

Given that individual systemic VEGF-A levels seem to be variable, a change of ±20% from baseline to study week 12 is considered clinically irrelevant. It is expected that the change of systemic VEGF-A protein levels from baseline to study week 12 following aflibercept treatment is >20%. A difference in change of ≥25% of systemic VEGF-A protein reduction between the two treatment arms from baseline to study week 12 is considered reasonable to show different effects of the two drugs on systemic VEGF-A plasma levels.
While the calculation of the sample size was performed using percentages due to the huge variability of baseline VEGF-A levels in the present data, it is assumed that the equivalent effect size will result from the area under the curve as endpoint variable.
A large standardized effect size of 1,25 was assumed (which would lead to an estimated common standard deviation of the change in VEGF-A levels of 20%). 15 patients per group are required to achieve 90% power on a 2-sided 5% significance level. To compensate for some dropouts and other protocol violations such as treatment of the fellow eye with anti-VEGF treatments, 20 patients per treatment arm (40 total) should be recruited into this trial.

As only baseline values and standard deviation for systemic VEGF-A levels are variable in all published studies to date, a blinded pooled analysis of the variance for the primary endpoint parameter will be performed when 20 patients (10 in each treatment arm) completed study

week 12. This analysis is intended to adjust the sample size if necessary while limiting the interventions (blood sampling) to as little patients as necessary.

10.8 Power for analysis of critical secondary variables

Not applicable.

11 Discussion and rationale for study design features

Study drug regimen and treatment design

Ranibizumab and aflibercept are both approved medications for the treatment of wAMD. They will be administered at the doses and according to the regimens recommended in the EU SmPC from baseline to study week 12. Thereafter, all patients will receive monthly ranibizumab injections.

Given that the sample size of the two study arms will be very small, application of a pro re nata regimen from study week 12 to study week 24 would result in very variable treatment patterns of the patients. Since this would limit the conclusions of this part of the study, monthly injection intervals were chosen.

At study week 12, patients in study group 2 will be switched from aflibercept to ranibizumab therapy in order to explore whether systemic VEGF levels adjust to levels comparable to baseline or to levels comparable as in patients treated with ranibizumab from baseline.

Randomization and Blinding

This is a single-blinded study where the investigator is not blinded to treatment but treatment assignment is randomized and consecutive enrollment will be used to help reduce bias. Given that the primary endpoint variable will be assessed by a blinded central laboratory, it is considered to be adequate that the injecting physician will not be blinded to treatment. The injecting physician has no influence on treatment regimen or primary or secondary endpoint assessments. A central laboratory and central reading center that is masked to treatment assignment will be used in order to ensure unbiased evaluation of the primary, secondary and exploratory objectives. The patient [redacted] are also blinded to treatment assignment.

Assessments

All study procedures related to the assessment of safety and efficacy are well established in the field of ophthalmologic clinical research or are non-invasive.

Interim analysis

There is only very little knowledge about the distribution of systemic VEGF-A levels and especially on the variability. Thus, as an over- or underestimation of the variance and consequently of the standardized effect size might jeopardize the adequacy of the planned sample size, a blinded pooled interim evaluation of the variance of VEGF-A levels is planned to possibly adapt the planned sample size only.

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Appendix 1: Ethical considerations and administrative procedures

Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

Responsibilities of the investigator and IRB/IEC/

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board / Independent Ethics Committee (IRB/IEC) before study start. Approval letters concerning protocol and informed consent will be filed by Novartis. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

Informed consent procedures

Eligible patients may only be included in the study after providing written, IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study.

Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days.

Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

Publication of study design and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities

Appendix 2: Clinically notable laboratory values and vital signs

Critical values for vital signs are defined in Table A2-1. Baseline critical values are defined by the absolute values only.

Table A2-1 Critical values

Variable	Type of abnormality	Critical values
Systolic blood pressure (mmHg)	High	Either >180 with an increase from baseline > 30 or > 200 absolute
	Low	Either < 90 with a decrease from baseline > 30 or < 75 absolute
Diastolic blood pressure (mmHg)	High	Either >105 with an increase from baseline > 20 or > 115 absolute
	Low	Either < 50 with a decrease from baseline > 20 or < 40 absolute
Pulse rate (bpm)	High	Either > 120 with an increase from baseline > 25 or > 130 absolute
	Low	Either < 50 with a decrease from baseline > 30 or < 40 absolute

Table A2-2 Criteria for the diagnosis of diabetes

WHO 2006	ADA 2014
Fasting plasma glucose ≥ 126mg/dL (7.0mmol/L)	
Or	
Two-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test	
n/a	Or
	HbA1c ≥ 6.5%
	Or
	In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).