Clinical Development

Ranibizumab; Lucentis®

Clinical Trial Protocol CRFB002AGB17 / NCT02161575

A Phase IV, prospective, open-label, uncontrolled, European **S**tudy in patients with neovascular **A**ge-related macular degeneration (nAMD), evaluating the efficacy and safety of switching **F**rom intravitreal **A**flibercept to **R**an**I**bizumab 0.5mg: the SAFARI study

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List of abbreviations

AE	Adverse event
AMD	Age-related macular degeneration
BCVA	Best-corrected visual acuity
CF	Color fundus photography
CNV	Choroidal neovascularization
CRC	Central reading center
CRT	Central retinal thickness
CSRT	Central subfield retinal thickness
CSRV	Central subfield retinal volume
DS&E	Drug Safety and Epidemiology
eCRF	electronic Case Report/Record Form
EOS	End of Study
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EWV	Early withdrawal visit
FA	Fluorescein angiography
FAF	Fundus autofluorescence
FAS	Full Analysis Set
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICGA	Indocyanine green angiography
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IN	Investigator notification
IOP	Intraocular pressure
IRC	Intra-retinal cysts
IUD	Intra-uterine device
IVT	Intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
nAMD	neovascular (wet) age-related macular degeneration
OCT	Optical Coherence Tomography
PCV	Polypoidal choroidal vasculopathy

PED	Pigment epithelial detachment
PFS	Pre-filled syringe
PRN	Pro re nata/administer as required
RAP	Retinal angiomatous proliferation
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SD/HD-OCT	Spectral domain/high definition optical coherence tomography
SF	Sub-retinal fluid
SmPC	Summary of Product Characteristics
SRT	Subfoveal retinal thickness
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom
VA	Visual acuity
VEGF	Vascular endothelial growth factor
WHO	World Health Organisation

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 at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
ETDRS - standards	Early Treatment Diabetic Retinopathy Study-standards became the standard for all subsequent ophthalmological clinical trials; they include specific guidelines and requirements on how BCVA is being assessed and the equipment to be used for this assessment
Fellow treated eye	The fellow eye treated with ranibizumab
Patient withdrawal	Point/time when the patient exits from the study before 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
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as Screening, Baseline, Monthly treatment, and PRN treatment
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Study drug	A drug administered to the patient as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy
Study eye	The study eye is the eye selected by the Investigator at Baseline (according to the protocol) to receive the study treatment
Subject number	A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Protocol summary

Protocol number	CRFB002AGB17
Title	A Phase IV, prospective, open-label, uncontrolled, European **S**tudy in patients with neovascular **A**ge-related macular degeneration (nAMD), evaluating the efficacy and safety of switching **F**rom intravitreal **A**flibercept to **R**an**I**bizumab 0.5mg: the SAFARI study
Brief title	Study of efficacy and safety of ranibizumab in patients with wet age related macular degeneration that have previously been treated with aflibercept.
Sponsor and Clinical Phase	Novartis Phase 4
Investigation type	Drug
Study type	Interventional
Purpose and rationale	There are limited prospective data regarding the potential benefit and risks associated with switching between anti-VEGF therapies in patients with nAMD who have either failed to achieve a clinical response to the first anti-VEGF therapy used, or who initially achieved a favorable response but subsequently have evidence of increasing disease activity despite continuation of therapy. Furthermore the retinal morphology characteristics of patients who respond favorably or unfavorably to an anti-VEGF switch strategy have not been previously reported. The purpose of this study is to determine, in patients with nAMD treated with aflibercept and where there is evidence of persistent or increasing disease activity, whether switching treatment to ranibizumab reduces disease activity over a 6 month period as assessed by a variety of measures including retinal imaging parameters and BCVA. [redacted]
Primary Objective(s)	The primary objective is to evaluate whether treatment with intravitreal ranibizumab is associated with improvement (i.e. reduction at Day 90 from Baseline) in central subfield retinal thickness (CSRT) as determined by spectral domain/high definition optical coherence tomography (SD/HD-OCT) after 3 monthly injections of ranibizumab. The CSRT represents the average retinal thickness (µm) of the circular area within 1 mm diameter around the foveal center.
Secondary Objectives	To evaluate whether treatment with intravitreal ranibizumab is associated with improvements in various retinal morphology parameters as determined by SD/HD-OCT at various time points over a period of 6 months and evaluated by the Central Reading Centre (CRC) including: • The change in subfoveal retinal thickness (SRT), central subfield retinal thickness (CSRT) and central subfield retinal volume (CSRV). • The proportion of patients with subretinal fluid (SF), intra-retinal cystoid changes (IRC), pigment epithelial detachments (PEDs),

	or dry retina. • The change in size (height or volume as appropriate) of various anatomical parameters including SF, IRC, and PEDs. To evaluate changes from Baseline BCVA at various time points over a period of 6 months including changes in BCVA between 3 and 6 months. To evaluate ocular and systemic safety by determining the incidence of ocular and systemic adverse events (AEs) up to Day 180.
Study design	This is a 6-month, phase IV, unmasked, uncontrolled, single arm, multicenter study. The study includes 8 study visits over a minimum of 6 months. All patients with nAMD and eligible to enter the study will receive 3 monthly intravitreal (IVT) ranibizumab 0.5mg injections followed thereafter by monthly IVT injections of ranibizumab 0.5mg on a PRN basis.
Population	The study will include 124 patients diagnosed with visual impairment due to nAMD who have been treated with aflibercept and where either no treatment response has been achieved or where there is suboptimal treatment response.
Key inclusion criteria	**Inclusion criteria for patient** • Age ≥50 years. • BCVA ≥23 ETDRS letters in study eye • Evidence of active CNV involving the center of the fovea in study eye **Patient subgroup specific inclusion criteria** Patients need to meet all the criteria for one of the following two groups: <u>Group 1. Primary treatment failure</u> • Initiated treatment with aflibercept <130 days prior to the Screening Visit. • No increase in BCVA (≥5 letters) since commencing treatment with aflibercept. • Disease activity has never been controlled in the study eye after initiating aflibercept as defined by at least one of the following: evidence of unchanged or increasing retinal* or sub-retinal fluid; new PED; unchanged or increasing size of pre-existing PED. <u>Group 2. Suboptimal treatment response</u> • Aflibercept commenced ≥6 months prior to the Screening Visit. • Received ≥3 aflibercept injections into the study eye within 6 months of the Screening Visit. • Evidence of previous reduced disease activity (as defined by reduction of ≥50µm in CSRT on OCT) noted in the study eye after initiating aflibercept. • At Screening Visit, disease activity has worsened (as defined by increasing retinal* or sub-retinal fluid, or new or increasing size of PED) in the study eye compared to prior visits.

	*Evidence of increasing retinal fluid may include increased number, size or total volume of IRCs, or increased central retinal or foveal thickness, or similar quantitative retinal imaging data recorded within the individual patient record.
Key exclusion criteria	**Exclusion criteria for systemic medical history and conditions** • History of cerebrovascular accident, transient ischemic attack or myocardial infarction within 3 months of the Screening visit. • Uncontrolled blood pressure **Exclusion criteria for ocular medical history and conditions for either eye** • Evidence of bilateral active CNV during the Screening Period or at Baseline requiring bilateral anti-VEGF injections*. • Prior intravitreal injection of ranibizumab or bevacizumab into the study eye and/or prior intravitreal injection of bevacizumab into the fellow eye. *Patients with active CNV in the study eye with quiescent CNV in the fellow eye who may have received IVT aflibercept or ranibizumab injections into the fellow eye >40 days prior to Screening, are not excluded from the Study. However, should the fellow eye require anti-VEGF treatment during the study, only ranibizumab may be utilized. **Study eye exclusion criteria** • Cataract (if causing significant visual impairment), aphakia, severe vitreous hemorrhage, rhegmatogenous retinal detachment, proliferative retinopathy or choroidal neovascularization of any other cause than wet AMD (e.g. ocular histoplasmosis, pathologic myopia (≥-6 dioptres)) at the time of Screening and Baseline. • Irreversible structural damage involving the center of the fovea (e.g. advanced fibrosis or geographic atrophy) which in the opinion of the Investigator is sufficient to irreversibly impair visual acuity. • Polypoidal choroidal vasculopathy (PCV), RPE tear, central serous retinopathy (CSR), or significant vitreomacular traction identified during Screening period or within 4 months of Baseline visit. Note that small vitreomacular adhesions that do not result in deformity of the retina are permitted. • Unable to obtain at Screening OCT images of sufficient quality to be analyzed.
Investigational and reference therapy	Investigational and reference therapy: The investigational treatment in this study is 0.5 mg ranibizumab. There is no reference therapy.
Efficacy assessments	Efficacy assessments will include both anatomical and functional evaluations. The methods of evaluation and the parameters to be assessed are listed below. • Spectral-domain/High definition Optical Coherence Tomography

	• ETDRS Best-Corrected Visual Acuity
Safety assessments	• Ophthalmic examinations • Vital signs • Adverse events
Other assessments	• Color fundus photography • Fluorescein angiography • Fundus autofluorescence • Indocyanine green angiography [redacted]
Data analysis	The primary objective is to demonstrate that the mean change from baseline in CSRT (as determined by SD/HD-OCT) at Day 90 is less than zero. [redacted] [redacted] The primary analysis will be performed on the Full Analysis Set.
Key words	Prospective, uncontrolled study, ranibizumab 0.5 mg, neovascular age-related macular degeneration, PRN, OCT, suboptimal treatment response, primary treatment failure

History of Amendments

Amendment 1

Amendment rationale

The main purpose for the current amendment is to update the requirements for historical OCT images during aflibercept treatment and add these to the inclusion criteria for further clarity.

In addition, references are included in the safety sections to the Investigator's Brochure as the Reference Safety Information, and minor corrections and clarifications have been made to the previous version of the study protocol.

The study started enrolment in the UK on 28th August 2014 and in Germany on 28th January 2015.

Changes to the Protocol

Major changes made to the protocol:

- Amendment to Sections 3.1, 4.1 (Inclusion criteria) and 6.4.1 to extend the time period for collection of pre-treatment historical OCT images from ≤ 14 days to ≤ 28 days before the date of first injection of aflibercept
- Amendment to Section 4.2: Study Eye Exclusion Criterion number 15 of the pathological myopia definition from ≥ 8 dioptres to ≥ 6 dioptres
- Clarification in Sections 3.6, 5.5.4, 7.1 and 7.2.2 that the Reference Safety Information for the study is the Investigator's Brochure for ranibizumab, rather than the SmPC

Additional minor and typographical changes (Sections 4.2: Exclusion Criterion number 12; Section 5.5; Section 6, Section 6.1, Section 6.4.1; Section 8.3; Section 9; Section 9.4.2)

Amendment 2

Amendment rationale

The main purpose for the current amendment is to re-assess the sample size calculation in the light of new information provided by a further literature search.

Changes to the Protocol

Major changes made to the protocol:

- Amendment to Protocol summary - Population, reducing the sample size from 162 to 124.
- Amendment to Section 4 (Population), reducing the sample size from 162 to 124 and consequently, the approximate number needing to be screened from 200 to 155.
- Amendment to Section 9.7 (Sample size calculation) reducing the estimated standard deviation of differences from 117 µm to 102 µm resulting in a reduction of the sample size from 162 to 124. Details regarding the justification of this change are also provided in this section.

1 Introduction

1.1 Background

Age-related macular degeneration (AMD) is the commonest cause of severe visual loss in people aged over 50 years in the UK and other European countries (Owen 2012). The prevalence of late AMD standardized to the UK population aged 50 years or more has been estimated to be 2.4%, increasing to 4.8% in those aged 65 years or more and 12.2% in those aged 80 years or more (Owen 2012). Given the demographic trend for an increasing proportion of elderly people in the European population, the prevalence of AMD will likely increase dramatically over the next decades (Klein 2004), resulting in significant morbidity and socioeconomic burden.

Two distinct forms of AMD exist, namely geographic atrophy (dry form) and choroidal neovascularization (wet or neovascular form, nAMD). Although nAMD accounts for only 10% of all AMD, 90% of people with severe visual loss have nAMD (Veritti 2012). The underlying processes and factors contributing to the etiology of nAMD are not entirely clear, although vascular endothelial growth factor (VEGF) has been identified as a key stimulus for angiogenesis, increase capillary permeability and disease progression for nAMD (Chong 2012).

The management of nAMD in Europe has been transformed since the availability of anti-VEGF therapies administered locally via intravitreous injection. Although pegaptanib was the first anti-VEGF available in 2006, many opthalmologists switched to using ranibizumab following regulatory approval in Switzerland in 2006 and European Commission approval in 2007. Unlike pegaptanib, ranibizumab demonstrated clinically and statistically significant improvements from baseline in visual acuity and patients' quality of life; improvements in visual acuity were rapid often occurring 7 days after the first intravitreous injection and sustained for at least 2 years (Rosenfeld 2006). Changes in visual acuity were also superior to the standard of care treatment at that time (verteporfin photodynamic therapy) and were also associated with significant improvements in the morphological characteristics of nAMD (Brown 2006).

Aflibercept is an anti-VEGF that was approved in 2012 by European competent authorities for use in nAMD. Two Phase 3 studies that supported approval of aflibercept for nAMD, evaluated changes in visual acuity with aflibercept as compared to ranibizumab (Heier 2012). Aflibercept 2mg treatment every 8 weeks after the initial 3 monthly doses, was demonstrated to be non-inferior and clinically equivalent to monthly ranibizumab 0.5mg with regards to improvement in visual acuity at 52 weeks (Heier 2012). Intravitreal aflibercept was generally well tolerated and had a profile of ocular treatment-emergent adverse events, including serious ocular adverse events, similar to those for monthly ranibizumab.

Despite the widespread use of intravitreal anti-VEGF therapies and evidence for improvement and stabilization of visual acuity for many patients, a minority of individuals experience rapid, continued worsening clinical status without ever having achieved an adequate clinical response (primary treatment failures), whilst in others there is evidence of persisting or worsening disease activity following an initial response to treatment (suboptimal treatment response). In these cases, repeated intravitreal injections may fail to stabilize either symptoms, visual acuity or other evidence of disease activity (CATT Research Group 2011; Fung 2012). Tachyphylaxis, where repeat administration of a drug leads to decreased therapeutic responses, has also been reported (Schaal 2008; Gasperini 2012). In all these cases, ophthalmologists are increasingly considering switching to an alternative anti-VEGF therapy.

1.2 Purpose

The purpose of this study is to determine, in patients with nAMD treated with aflibercept and where there is evidence of persistent or increasing disease activity, whether switching treatment to ranibizumab 0.5mg reduces disease activity over a 6 month period as assessed by a variety of measures.

2 Study objectives

2.1 Primary objective

The primary objective is to evaluate whether treatment with intravitreal ranibizumab 0.5mg is associated with improvement (i.e. reduction at Day 90 from Baseline) in central subfield retinal thickness (CSRT) as determined by optical coherence tomography (OCT) after 3 monthly injections of ranibizumab.

2.2 Secondary objectives

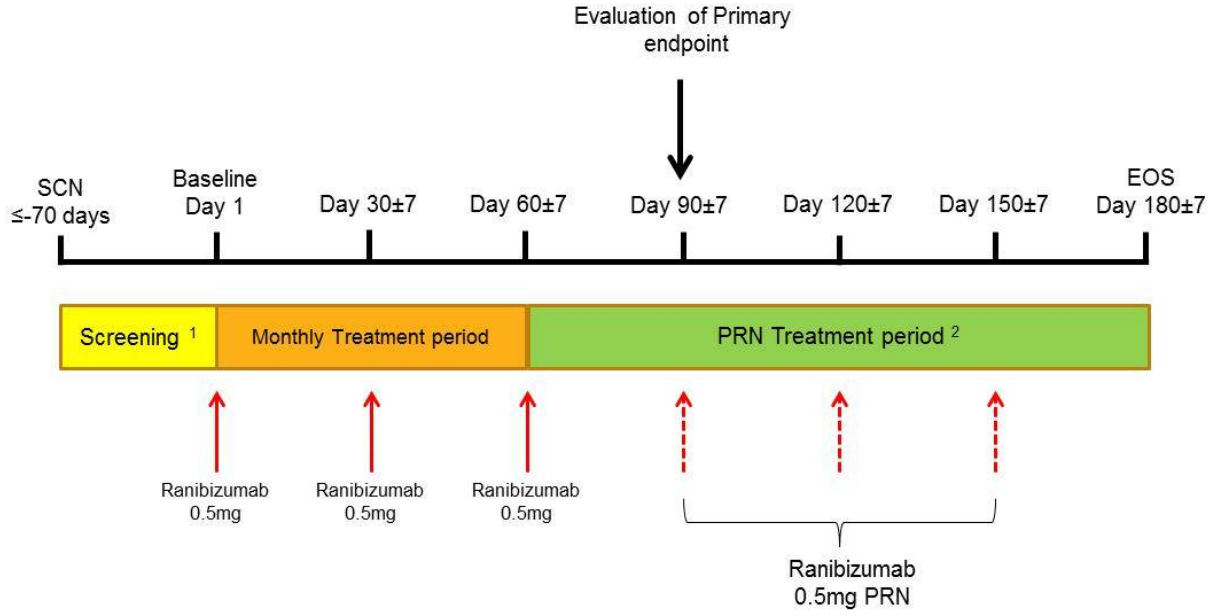
- To evaluate whether treatment with intravitreal ranibizumab 0.5mg is associated with improvements in various retinal morphology parameters as determined by OCT at various time points over a period of 6 months and evaluated by a Central Reading Centre (CRC), including:
    - The change in subfoveal retinal thickness (SRT), central subfield retinal thickness (CSRT) and central subfield retinal volume (CSRV).
    - The proportion of patients with subretinal fluid (SF), intra-retinal cystoid changes (IRC), pigment epithelial detachments (PEDs), or dry retina.
    - The change in size (height or volume as appropriate) of various anatomical parameters including SF, IRC, and PEDs.
- To evaluate changes from Baseline BCVA at various time points over a period of 6 months including changes in BCVA between 3 and 6 months.
- To evaluate ocular and systemic safety by determining the incidence of ocular and systemic adverse events (AEs).

3 Investigational plan

3.1 Study design

This is a 6-month, phase IV, unmasked, uncontrolled, single arm, multicenter study. The study includes 8 study visits over a minimum of 6 months. All patients with nAMD and eligible to enter the study will receive 3 monthly intravitreal (IVT) ranibizumab 0.5mg injections followed thereafter by monthly IVT injections of ranibizumab 0.5mg on a PRN basis (Figure 3-1).

Figure 3-1 Study design



There will be 3 periods in this study;

- Screening period: from Day -70 to Day 0
- Monthly Treatment period: from Baseline (Day 1) to Day 60
- PRN Treatment period: from Day 61 to Day 180

Screening Period: Day -70 to Day 0

At the Screening visit, patient informed consent will be obtained and eligibility criteria will be assessed. The informed consent process will also include providing consent for prior medical and treatment history, as well as for pseudo-anonymized historical retinal images to be reviewed by a Central Reading Centre (CRC). [redacted]

After signing the informed consent, several procedures will be performed to assess eligibility (patient and study eye). For the study eye eligibility, BCVA, ophthalmic examination, SD/HD-OCT, color fundus photography (CF), fluorescein angiography (FA), indocyanine green angiography (ICGA) and fundus autofluorescence (FAF) will be performed. The study eye will be selected at the discretion of the Investigator to be used for the primary, secondary [redacted] based on the eligibility criteria defined in Section 4. Various retinal and choroidal imaging assessments for the study eye should be completed and transferred to the CRC (Figure 3-1 and Table 6-1). [redacted] In addition, pseudo-anonymized historical retinal OCT images acquired after a minimum of 2 aflibercept injections indicating either no change or worsening disease activity (primary treatment failure subgroup) or an improvement in retinal morphology (suboptimal treatment response subgroup) will also be collected and transferred to the CRC. Patients that do not meet the eligibility criteria on the first occasion may undergo rescreening on 1 more occasion only. Eligibility for inclusion within the study will be performed at a site level and not by the CRC.

For patients meeting the eligibility criteria for primary treatment failure to aflibercept (see Section 4.1 for definitions), a minimum of 28 days but no more than 40 days should have passed since the last IVT injection of aflibercept before the Baseline Visit (Day 1) occurs. The source data will need to verify the patient fulfils eligibility criteria for this subgroup.

For patients meeting the eligibility criteria for suboptimal treatment response to aflibercept (see Section 4.1 for definition), a minimum of 28 days but no more than 70 days should have passed since the last IVT injection of aflibercept before the Baseline Visit (Day 1) occurs. The source data will need to verify the patient fulfils eligibility criteria for this subgroup.

[redacted]

Monthly Treatment period: Day 1 to Day 60

Eligibility criteria will be confirmed by the Investigator at Baseline and BCVA, retinal and choroidal imaging, and pre-therapy adverse events will be evaluated before the first IVT injection of ranibizumab 0.5mg. [redacted] Repeat efficacy and safety assessments (see Table 6-1) and IVT ranibizumab injections will occur at Day 30 and Day 60 visits. Injections of IVT ranibizumab to the study eye should occur on the same day as the scheduled study visit.

All subjects will attend Scheduled Study Visits every 30 (±7) days.

PRN treatment period: Day 61 to Day 180

Efficacy and safety assessments will be repeated (see Table 6-1) at Day 90, 120, 150 and 180. All subjects will attend Scheduled Study Visits every 30 (±7) days. The primary endpoint will be evaluated when patients have completed assessments at the Day 90 visit.

Between the Day 90 and Day 150 visits inclusive, the decision to administer ranibizumab 0.5mg will be at the discretion of the Investigator and driven either by persistent or worsening visual symptoms attributed by the Investigator to nAMD, or worsening visual acuity (>1 letter decline since last Study Visit) or by the presence of persistent or worsening disease activity on OCT*. Source documentation must provide evidence for one or more of these retreatment criteria. Injections of IVT ranibizumab to the study eye, where required, should occur on the same day as the scheduled study visit.

Final efficacy and safety assessments will be conducted at Day 180.

* Persistent or worsening disease activity on OCT includes the presence of sub-retinal fluid, persistent or increased number, size or total volume of IRCs, or increased central retinal or foveal thickness, or similar quantitative retinal imaging data recorded within the individual patient record.

3.2 Rationale of study design

This study can be considered exploratory in nature as there are no published data describing the efficacy of switching treatment from aflibercept to ranibizumab in patients with nAMD where either no treatment response has been achieved or where there is suboptimal treatment response. It is recognized that there are potential patient and Investigator derived sources of bias in this study due to the unmasked design, but these are acceptable bearing in mind the exploratory nature of the study. A parallel group design to include either a sham injection group or continued injection of aflibercept cannot be justified at this stage as the patient population most likely to benefit from a switch from aflibercept to ranibizumab is unknown and there are insufficient data to assist in the development of sample size calculations that allow robust statistical conclusions to be achieved on potential between group differences.

The design of the study also reflects current clinical practice where patients who achieve suboptimal treatment responses with one anti-VEGF therapy will be switched to an alternative anti-VEGF therapy. The 6 month duration of the study is also reflective of the timeframe used in clinical practice to assess whether patients are likely to achieve a meaningful clinical response to an anti-VEGF therapy.

3.3 Rationale of dose/regimen, route of administration and duration of treatment

In this study, ranibizumab will be administered at the SmPC and other product labels approved dose of 0.5mg and the dosing regimen is consistent with current clinical practice where re-treatment decisions are based not only on changes in VA but also on retinal morphology changes that may be indicative of disease activity (Myolonas 2009). Historical data from a number of clinical trials demonstrate that 0.5mg ranibizumab offers a favorable benefit-risk profile. Ranibizumab is administered as an IVT injection to maximize the bioavailability of the drug at the site of pathology while minimizing systemic exposure.

The posology section of the SmPC for ranibizumab recommends monthly injections until maximum visual acuity is achieved with additional injections thereafter in the event of a loss of visual acuity due to nAMD. In this study, this re-treatment criterion will be applied although in addition re-treatment will occur based on measures of increasing or persistent retinal disease activity as these are commonly used in clinical practice. The permitted interval between ranibizumab injections will be 23 to 37 days during the Monthly Treatment period and 23 days or greater during the PRN Treatment period. This study design is in keeping with the posology used in other prospective studies with ranibizumab in nAMD.

3.4 Rationale for choice of comparator

No comparator will be used in this study.

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis will be conducted after the first 50 patients complete the 90 day study visit. The primary objective for this analysis is to provide preliminary safety data in the proposed population of patients with nAMD. The secondary objective is to provide preliminary efficacy data.

3.6 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures and close clinical monitoring. The management and monitoring of patients in this study reflects both the recommendations within the IB, SmPC, other international product labelling, and current clinical practice; there are no clinically relevant disadvantages from participating in this study. The risks associated with use of ranibizumab are well described in the IB, product labelling and patient information leaflet.

Patients who provide informed consent and enter this study, are currently not achieving optimal treatment response with aflibercept. The potential benefit to participants is that disease activity may be stabilized or improved with ranibizumab.

4 Population

The study will include patients diagnosed with visual impairment due to nAMD who have been treated with aflibercept and where either no treatment response has been achieved or where there is suboptimal treatment response. Assuming an approximate 20% screen failure rate, approximately 155 patients will need to be screened to have 124 eligible patients commencing treatment in the trial. Approximately 40 ophthalmology centers in Western European countries will be initiated.

It is anticipated that patients with primary treatment failure to aflibercept (see Section 4.1 for definition) are likely to achieve small responses to treatment with ranibizumab. In order to minimize potential risks to these patients, a maximum of 30 patients will be recruited in this subgroup.

4.1 Inclusion criteria

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

Inclusion criteria for patient

1. Written informed consent must be obtained before any assessment is performed.
2. Age ≥50 years.
3. BCVA ≥23 ETDRS letters, at both the Screening Visit and Baseline Visit in the Study eye.
4. Active, angiographically documented CNV lesion in study eye (e.g. leakage on fluorescein angiography plus intraretinal, subretinal or sub-retinal pigment epithelium (RPE) fluid on SD/HD-OCT) secondary to AMD at Screening.

5. Evidence of active CNV involving the center of the fovea in the study eye (e.g. pigment epithelium detachment, subretinal or sub-RPE hemorrhage, macular edema, or subretinal, sub-RPE or intraretinal fluid) at Baseline.
6. The total area of fibrosis in the study eye comprising less than 50% of the lesion area.

Patient subgroup specific inclusion criteria
Patients need to meet all the criteria for one of the following two groups:

Group 1. Primary treatment failure

7. No prior anti-VEGF treatment prior to initiating aflibercept.
8. Received no more than 3 injections of aflibercept into the study eye prior to the Screening Visit.
9. Historical OCT volume scan acquired ≤28 days before the first aflibercept injection was administered to the study eye.
10. Initiated treatment with aflibercept <130 days prior to the Screening Visit.
11. Last injection of aflibercept was ≥28 days but ≤40 days prior to the Baseline visit.
12. No increase in BCVA (≥5 letters) since commencing treatment with aflibercept.
13. Disease activity has never been controlled in the study eye after initiating aflibercept as defined by at least one of the following observed on a historical OCT volume scan acquired after a minimum of 2 aflibercept injections: evidence of unchanged or increasing retinal* or sub-retinal fluid; new PED; unchanged or increasing size of pre-existing PED.

Group 2. Suboptimal treatment response

14. No prior anti-VEGF treatment prior to initiating aflibercept.
15. Aflibercept commenced ≥6 months prior to the Screening Visit.
16. Received ≥3 aflibercept injections into the study eye within 6 months of the Screening Visit.
17. Historical OCT volume scan acquired ≤28 days before the first aflibercept injection was administered to the study eye.
18. Evidence of previous reduced disease activity in the study eye after initiating aflibercept as defined by reduction of ≥50µm in central subfield retinal thickness observed on a historical OCT volume scan acquired after a minimum of 2 aflibercept injections.
19. Last injection of aflibercept was ≥28 days but ≤70 days prior to the Baseline visit.
20. At Screening Visit, disease activity has worsened (as defined by increasing retinal* or sub-retinal fluid, or new or increasing size of PED) in the study eye compared to prior visits.

* Evidence of increasing retinal fluid may include increased number, size or total volume of IRCs, or increased central retinal or foveal thickness, or similar quantitative retinal imaging data recorded within the individual patient record

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the Investigator, in order to ensure that the study population will be representative of all eligible patients.

Exclusion criteria for patient

1. Inability to comply with study or follow-up procedures.
2. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
3. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female subjects in the study, the vasectomized male partner should be the sole partner for that subject.
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS).

    In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Exclusion criteria for systemic medical history and conditions

4. History of cerebrovascular accident, transient ischemic attack or myocardial infarction within 3 months of the Screening visit.
5. 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.
6. Uncontrolled blood pressure defined as a persistent systolic value of >160 mm Hg or persistent diastolic value of >100 mm Hg at Screening or Baseline.
7. Simultaneous participation in any other clinical study for the duration of this study.
8. Use of other investigational drugs (excluding vitamins and minerals) or participation in any other clinical study within 90 days or 5 half-lives of the Screening visit, or until the expected pharmacodynamic effect has resolved, whichever is longer.
9. History of hypersensitivity to either ranibizumab (or any component of the ranibizumab formulation), or fluorescein, or indocyanine green, or to drugs of similar chemical classes.

Exclusion criteria for ocular medical history and conditions

For either eye

10. Any active periocular or ocular infection or inflammation (e.g., blepharitis, conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) at the time of Screening or Baseline.
11. Uncontrolled glaucoma (intraocular pressure [IOP] ≥30 mm Hg on medication or according to Investigator's judgment) at the time of Screening or Baseline.
12. Evidence of bilateral active CNV during the Screening Period or at Baseline requiring bilateral anti-VEGF injections. Patients with active CNV in the study eye with quiescent CNV in the fellow eye who may have received IVT aflibercept or ranibizumab injections into the fellow eye >40 days prior to the Screening visit are not excluded from the study; however, should the fellow eye require anti-VEGF treatment during the study only ranibizumab may be utilized.
13. Prior intravitreal injection of ranibizumab or bevacizumab into the study eye and/or prior intravitreal injection of bevacizumab into the fellow eye

Study eye exclusion criteria

14. At Baseline, intraocular surgery was performed within the previous 28 days or intraocular surgery is planned at any time during the 6 month study period.
15. Cataract (if causing significant visual impairment), aphakia, severe vitreous hemorrhage, rhegmatogenous retinal detachment, proliferative retinopathy or choroidal neovascularization of any other cause for CNV other than wet AMD (e.g., ocular histoplasmosis, pathologic myopia (≥-6 dioptres)) at the time of Screening and Baseline.
16. Irreversible structural damage involving the center of the fovea (e.g. advanced fibrosis or geographic atrophy) which in the opinion of the Investigator is sufficient to irreversibly impair visual acuity.

17. Polypoidal choroidal vasculopathy (PCV), RPE tear, central serous retinopathy (CSR), or significant vitreomacular traction identified during Screening period or within 4 months of Baseline visit. Note that small vitreomacular adhesions that do not result in deformity of the retina are permitted.
18. Any other ocular abnormality unrelated to AMD that is in the Investigator's opinion is likely to contribute to progressive deterioration in visual acuity over the next 6 months.
19. Prior laser therapy or use of verteporfin photodynamic therapy.
20. Prior use of intra- or peri-ocular corticosteroids within 6 months of Screening.
21. Unable to obtain at Screening SD/HD-OCT images of sufficient quality to be analyzed.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

The investigational treatment/study drug in this study is ranibizumab 0.5mg (Lucentis®).

Ranibizumab solution for injection will be supplied in either pre-filled syringes (PFS) or vials according to local availability. Each PFS or vial contains ranibizumab in a concentration of 10mg/ml (labeled as RFB002 0.5mg/0.05ml, corresponding to a 0.5mg dose).

Study medication will be supplied in commercially available packaging. Each vial or PFS will be labeled with the appropriate information. Medication labels will comply with the legal requirements and be printed in the local language. The storage conditions will be described on the label.

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile glass vial or PFS. Each vial/PFS contains ranibizumab in an aqueous solution (pH 5.5) with histidine, trehalose and polysorbate 20. The vial/PFS contains no preservatives. It is suitable for single use only and the content of the vial/PFS must not be split. Ranibizumab must be stored according to label instructions and it must be kept in a secure locked facility.

5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

5.2 Treatment arms

All eligible patients will be assigned to active treatment with ranibizumab.

5.3 Treatment assignment, randomization

This is not a randomized study. Patients will meet eligibility criteria for either the primary treatment failure subgroup or the secondary suboptimal response subgroup (see Section 4.1). Recruitment of patients into the primary treatment failure subgroup will be up to a maximum of 30 patients. Recruitment to this subgroup will be closed once this number of patients has been allocated to the primary treatment failure subgroup, and have both successfully completed the Screening assessments and confirmation of eligibility has been entered into the eCRF.

At the Baseline Visit (Day 1), all eligible patients will receive IVT injection of ranibizumab 0.5mg into the study eye. Repeat ranibizumab injections will only occur at scheduled study visits; i.e. at Day 30 (±7) and Day 60 (±7). Repeated ranibizumab injections may also occur according to the protocol defined re-treatment criteria (see Section 5.5.4) at Day 90 (±7) and Day 120 (±7). After each visit has been performed the eCRF needs to be updated with the details of whether an injection has been administered or not.

5.4 Treatment masking

This is an open-label study and neither Investigators nor patients are masked.

5.5 Treating the patient

5.5.1 Subject numbering

Each patient is uniquely identified in the study by a combination of his/her center number and subject number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a subject number by the Investigator. At each site, the first patient is assigned subject number 01, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned subject number 02, the third patient is assigned subject number 03). Once assigned to a patient, the subject number will not be reused. This also applies to the situation in which a patient has initially failed screening but at a later stage meets all eligibility criteria. It is then possible to re-screen the same patient but a new subject number has to be assigned. As long as the recruitment phase has not yet ended, re-screening (on one occasion only) is possible.

The site should enter the data into the eCRF for that patient using the individual subject number. Only the assigned subject number should be entered in the field labeled “Patient ID” on the eCRF data entry screen (e.g. enter ‘01’, ‘02’, etc.). If the patient undergoes screening but fails to meet the eligibility criteria, the reason(s) will be entered on the Screening Log and the Demography eCRF should be completed.

If the patient is eligible for treatment but fails to be treated at the Baseline visit for any reason, the reason(s) for not being treated should be entered on the Screening Log and the Demography eCRF should be completed. Re-screening (on one occasion only) may be possible for these patients.

5.5.2 Dispensing the investigational treatment

Within each participating country, each study site will be supplied by Novartis with investigational treatment (study drug) in commercially available packaging, labelled according to local legal requirements. The decision to administer study drug to the patient is made according to the protocol specified treatment regimen.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational treatment (study drug) 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 the Investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the patient.

The Investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. All used vials/PFS packaging should be kept until monitoring of drug accountability has been completed by the field monitor. 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 unused investigational treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

5.5.3.2 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

For the entire trial, ranibizumab should be administered in the study eye on the day of the scheduled study visit. In the event that a protocol specified ranibizumab injection into the study eye is delayed for more than 7 days following the scheduled study visit, a protocol deviation will be recorded but the patient may continue in the study. The assessments required as part of an Unscheduled Visit should be conducted and recorded in the eCRF (see Section 6). The Investigator should make every effort to resume the protocol specified timings for scheduled study visits and simultaneous ranibizumab injections to the study eye. Repeat ranibizumab injection into the study eye may not be administered sooner than 23 days after the last ranibizumab injection into the study eye.

Instructions on how to prepare and administer ranibizumab for IVT injection using the PFS or vial should follow the locally approved product information leaflet. Details of all PFS and vials administered will be recorded in the eCRF. Standard local practice should be applied in the peri-injection management of patients and should be consistent with the local labelling and/or IB.

The injection procedure should be carried out under aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape and a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required). Adequate anesthesia and a broad-spectrum topical microbicide to disinfect the periocular skin, eyelid and ocular surface may be administered prior to the injection, in accordance with local practice. The injection needle should be inserted 3.5-4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming towards the center of the globe. The injection volume of 0.05 ml is then delivered; a different scleral site should be used for subsequent injections. Both intraocular pressure and the perfusion of the optic nerve head must be monitored and managed appropriately following IVT injection of ranibizumab.

5.5.4.1 Monthly Treatment Period: Day 1 to Day 60

After eligibility confirmation at Baseline (Day 1), all patients will receive IVT injection of ranibizumab into the study eye. Re-treatment with IVT injection of ranibizumab will occur on Day 30 and Day 60.

5.5.4.2 PRN Treatment Period: Day 90 to Day 180

All patients will have monthly assessments of BCVA and disease activity assessed by OCT. These assessments, together with an assessment of the patient's visual symptoms, will be used for the decision of potential re-treatment with ranibizumab. This PRN regimen, will permit re-treatment with ranibizumab at Day 90, Day 120 and/or Day 150 if in the opinion of the Investigator persistent or worsening visual symptoms are attributed to nAMD, and/or if there is evidence of worsening ETDRS best corrected visual acuity (>1 letter decline since last Study Visit) and/or the presence of persistent or worsening disease activity on OCT*. Source documentation must provide evidence for one or more of these retreatment criteria.

5.5.4.3 Treatment of the Fellow Eye

Patients who develop visual impairment due to nAMD in the fellow eye (non-study eye) during the study 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, including ocular administration with ranibizumab. This eye is then called the fellow treated eye.

Ranibizumab will be provided by the Sponsor (supplied for investigational treatment) and should be administered according to the SmPC or local labelling. Details of all PFS and vials administered will be recorded on drug accountability forms and a record of the administration also included in the eCRF.

Treatment of the fellow eye must be scheduled in a way not to disturb the schedule for visits and treatments of the study eye. Ideally injection of the fellow eye should occur on the same day as a scheduled study visit in order to minimize the total number of clinic visits required by the patient. Bilateral IVT injections of ranibizumab may occur at any scheduled study visit between Day 30 and Day 150. The fellow treated eye must be monitored according to routine practice and AE(s) and SAE(s) must be captured in the eCRF. Should injection of the fellow eye occur at a visit other than a scheduled study visit, this should be recorded in the eCRF as an unscheduled study visit and all protocol specified procedures for an unscheduled visit should be completed (see Section 6).

If in the Investigator's opinion, the fellow eye requires further treatment with ranibizumab, this should not occur more frequently than monthly in accordance with the posology section of the SmPC. A protocol deviation will be recorded should the patient receive a repeat ranibizumab injection into the fellow eye less than 23 days after the previous injection into the fellow eye. However, the patient will not be withdrawn from the study.

At the time when treatment of the fellow eye is being initiated, the BCVA assessment for the fellow eye should be repeated and recorded in the eCRF.

Treatment with other anti-VEGF medication other than ranibizumab is prohibited in either eye at any time during the study.

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* Persistent or worsening disease activity on OCT includes the presence of sub-retinal fluid, persistent or increased number, size or total volume of IRC, or increased central retinal or foveal thickness, or similar quantitative retinal imaging data recorded within the individual patient record.

Treatment for non-nAMD indications with anti-angiogenic drugs including ranibizumab in the fellow eye is prohibited.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Dose adjustments, i.e., adjustments of the injection volume of ranibizumab dose solution, are not permitted. Adjustments of the PRN dosing regimen of ranibizumab that is described as part of the study treatment administration in Section 3.1, and Section 5.5.4 are not permitted.

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

- an IOP of ≥30 mm Hg,
- an untreated retinal tear is diagnosed,
- active or suspected ocular or periocular infections,
- active severe intraocular inflammation.

5.5.6 Rescue medication

No rescue medication is permitted in this study.

5.5.7 Concomitant treatment

The Investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications (including for non-ophthalmic conditions), 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 eCRF.

Medications that may be used as part of the protocol specified retinal image acquisition (e.g., mydriatic drops, fluorescein dyes) and pre- and post-injection medications (e.g., topical anesthetics, topical antimicrobials) used by a patient during the study, are not considered concomitant medications.

If a patient requires intraocular surgery on the study eye during the course of the study, the patient should be withdrawn from the study.

5.5.8 Prohibited Treatment

Use of treatments, as displayed in Table 5-1 is NOT allowed after the Screening visit and for the duration of the study. In addition, there are certain wash-out periods to be respected as outlined in the list of exclusion criteria.

Please see Table 5-1 below for actions to be taken, apart from stopping the prohibited medication taken.

Table 5-1 Prohibited treatment

Medication	Action to be taken
Anti-VEGF drugs other than ranibizumab (ocular or systemic)	Withdraw patient from study
Intra- or periocular corticosteroids (including sub-tenon but excluding topical formulations) – study eye only	Withdraw patient from study
Intra-ocular corticosteroid implants – study eye only	Withdraw patient from study
Investigational drugs and interventions of any type	Withdraw patient from study

5.5.9 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time.

The study and treatment completion dates will be determined by the last visit the patient came to the clinic.

The Investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

Patients can discontinue study treatment because of the appearance of a new health condition suspected to require appropriate care or require medications prohibited by the protocol (Section 5.5.8), unacceptable AEs, refusal to continue treatment, or at the Investigator's discretion based on his or her clinical judgment.

The Investigator should discontinue study treatment for a given patient or withdraw the patient from study if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued under the following circumstances:

- Withdrawal of informed consent
- Emergence of the following AEs:
    - Stage 3 or 4 macular hole
    - Stroke or transient ischemic attack
    - Rhegmatogenous retinal detachment
- Pregnancy
- Use of prohibited treatment in Table 5-1
- Two sequential ranibizumab injections to the study eye should have occurred according to the protocol specified monthly/PRN treatment period criteria but were withheld (see Section 5.5.5) or missed.

- Any other protocol deviation that results in a significant risk to the patient's safety.

Patients who permanently discontinue study treatment and start a prohibited non-study treatment (see Section 5.5.8) should be withdrawn from the study and undergo all assessments for End of Study visit as described in Table 6-1 and Table 6-2.

Patients who discontinue study treatment but do not receive prohibited treatment should not be considered withdrawn from the study and may continue their scheduled follow-up assessments until End of Study.

The Completion/Withdrawal eCRF page should be completed, providing the primary reason for stopping study treatment.

5.5.10 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore and does not want any further visits or assessments and does not want any further study related contacts and does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the Investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the eCRF. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

The Completion/Withdrawal eCRF page should be completed, providing the primary reason for stopping study treatment.

5.5.11 Loss to follow-up

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 the steps taken to contact the patient (e.g., dates of telephone calls, registered letters).

The Completion/Withdrawal eCRF page should be completed, providing the primary reason for stopping study treatment.

5.5.12 Emergency breaking of assigned treatment code

Not applicable as all patients will receive ranibizumab 0.5mg

5.5.13 Study completion and post-study treatment

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

Patients who successfully complete all study assessments of the study through to Day 180 will be considered to have completed the study.

The study is considered as completed once, according to the study protocol, all protocol required activities have been executed in all treated patients.

No extension study has been planned.

Following completion of the study, all patients will be provided with appropriate ongoing care according to the Investigator's or treating ophthalmologist's judgment.

5.5.14 Early study termination

The study can be terminated at any time and for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as described in Section 6 for a prematurely withdrawn patient. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing the local IEC of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 and Table 6-2 list all the assessments and procedures to be performed by study visits.

All data obtained from these assessments must be supported in the patient's source documentation. Assessments are indicated with an "X" when they need to be performed.

A planned study visit schedule will be established at the time of Baseline visit (Day 1) for all patients. Study assessments will be performed at the Screening visit, Baseline (Day 1), and at Day 30, Day 60, Day 90, Day 120, Day 150 and Day 180, ± 7 days to allow for flexibility in scheduling. In addition, the Screening visit may be performed over a maximum of 2 consecutive days; if this occurs, the last day must be entered as the visit date in the eCRF

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 treatments which should be ≥ 23 days.

At a minimum, patients will be contacted and reviewed in the clinic for safety evaluations either at Day 180 (±7) days, or during the 30 days following the last administration of study treatment. Documentation of attempts to contact the patient should be recorded in the source documentation.

Should unscheduled study visits occur, the Investigator will ask the patient for information regarding the use of concomitant medications and new or ongoing adverse events, which will be recorded in source documentation and in the eCRF. BCVA for both eyes, vital signs and ranibizumab injections that occur at unscheduled study visits will also be recorded in the eCRF.

Table 6-1 Assessment schedule (Eligibility criteria, demographics & baseline characteristics, imaging procedures)

	Screening V1	Baseline V2	V3	V4	PEV V5	V6	V7	EOS or EWV V8	UNSCHED V
Days relative to Day 1 (permitted time window)	Primary treatment failure≤40 days Suboptimal treatment response≤70 days prior to Baseline visit	1	30±7	60±7	90±7	120±7	150±7	180±7	
Informed consent	X								
Review of inclusion/exclusion criteria	X	X							
Diagnosis	X								
Demography	X								
Medical History	X	X							
Prior/concomitant meds	X	X	X	X	X	X	X	X	X
Serum pregnancy test	X								
BCVA score (ETDRS)	X*	X*	X	X	X*	X	X	X*	X*
Historical retinal images collected	X								
Ophthalmic examination	X	X	X	X	X	X	X	X	
OCT (retina and choroid)	X	X	X	X	X	X	X	X	
Color fundus photography	X							X	
Fluorescein angiography	X							X	
Fundus autofluorescence	X							X	
Indocyanine green angiography	X								

PEV: Primary Endpoint Visit. EOS: End of Study visit also incorporates the Early Withdrawal Visit (EWV). UNSCHED V: Unscheduled visit
* Assessment to be performed also on fellow-eye; where ranibizumab treatment is initiated in the fellow-eye BCVA is to be repeated and recorded in the eCRF prior to injection.

Table 6-2 Assessment schedule (peri-injection procedures, safety assessments and venous blood sample collection)

	Screening V1	Baseline V2	V3	V4	PEV V5	V6	V7	EOS or EWV V8	UNSCHED V
Dispense topical antibiotic medication according to local practice		(X)	(X)	(X)	(X)	(X)	(X)		
Ranibizumab injection		X	X	X	(X)	(X)	(X)		
Post-injection assessments		X	X	X	(X)	(X)	(X)		
Vital signs	X	X	X	X	X	X	X	X	X
Height and Weight	X								
Adverse events	X	X	X	X	X	X	X	X	X
[redacted]									

PEV: Primary Endpoint Visit. EOS: End of Study visit also incorporates the Early Withdrawal Visit (EWV). UNSCHED V: Unscheduled visit
(X) Indicates that local standard practice should be applied or in the case of ranibizumab injection, that Investigator judgment is used to determine whether repeat injection is required.

6.1 Information to be collected on screening failures

All patients who have signed informed consent but not initiated study treatment at Baseline will be considered Screen Failures. For these patients demographics, inclusion/exclusion fulfillment, and adverse event (AE) data will be collected. The Completion/Withdrawal page in the eCRF will be completed.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristics to be collected on screened patients include:

- Demography: year of birth, gender, race, ethnicity
- Relevant medical history/current medical condition data includes data until the informed consent form is signed. Where possible, diagnoses and not symptoms will be recorded. Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever the test abnormality occurred before the informed consent signature
- Study eye selection
- Baseline characteristics
- Prior utilization of aflibercept (number and dates of injections into one or both eyes)
- Other assessments performed at Screening to determine eligibility are listed in Table 6-1.

At the Baseline visit and after review of eligibility criteria, patients will be allocated to either the primary treatment failure subgroup or to the suboptimal treatment response subgroup.

6.3 Treatment exposure and compliance

Treatment exposure

Treatment exposure to ranibizumab will be assessed for both study eye and fellow treated eye as well as total exposure (study eye and fellow eye). Information regarding study treatment administration (ranibizumab) in the study eye will be collected on the drug administration record eCRF. Treatment of the fellow eye with ranibizumab will be captured on a separate eCRF.

The reason for dosing of ranibizumab or the reason for dose/no dose will be described on the drug administration record eCRF for the study eye.

At every visit, it needs to be reported within the eCRF if treatment or no treatment with study drug has been administered to the patient both for the study eye and the fellow eye.

In addition, confirmation of disease activity as assessed by the Investigator through functional and anatomical parameters detected by BCVA and OCT will be captured for the study eye (please see Section 5.5.4.2).

Compliance to treatment regimen

The evaluation of compliance will assess whether ranibizumab injections were administered according to the protocol specified regimen during the monthly treatment period and according to the Investigator's assessment of disease activity during the PRN treatment period.

6.4 Efficacy

All efficacy assessments are to be performed on the study eye and recorded in the eCRF. Efficacy assessments will include both functional and anatomical evaluations. The methods of evaluation and the parameters to be assessed are described below.

These assessments are performed according to the schedule in Table 6-1 and Table 6-2.

Study eye selection:

The Investigator will designate the study eye based on the pre-specified eligibility criteria at the Screening visit and will confirm his/her decision at the Baseline visit. As described in Section 4.2, patients are ineligible to participate in the study if there is evidence of bilateral active CNV at Baseline requiring bilateral anti-VEGF treatment. The decision as to the selection of the study eye needs to be documented in the eCRF and in the source documents of the patient. The study eye is the one treated with the study treatment, assessed according to protocol requirements and as outlined in the assessment schedule (Table 6-1 and Table 6-2) and data collected on the study eye are used for the evaluation of efficacy objectives of the study. At visits when ranibizumab treatment is administered, efficacy assessments must be conducted prior to administration of ranibizumab.

At all visits where efficacy assessments are conducted, BCVA should be assessed first before mydriatic drops are applied to the study eye in order to acquire ophthalmic images.

6.4.1 Optical Coherence Tomography

Optical Coherence Tomography (OCT) images are to be taken using High Definition (HD)/Spectral Domain (SD) optical coherence tomography (OCT) equipment. Patients must be assessed using the same machine throughout the course of the study.

The Investigator will perform OCT at visits indicated in Table 6-1 according to a standardized imaging protocol as specified in the Procedure Manual. The information collected will be used by the Investigator to assess the status of disease activity; i.e., decisions on subject eligibility as well as decisions on PRN treatment are based on his/her own evaluation.

The Investigator will send the digital raw images taken monthly from Screening to Day 180 to the Central Reading Center (CRC) as soon as possible after the Scheduled Study Visit; the images will be transferred electronically using the dedicated SD/HD-OCT software format. No transmission of imaging data on print-outs will be accepted. The captured images will contain quantitative parameters (i.e., the Subfoveal Retinal Thickness (SRT), the Central Subfield Retinal Thickness (CSRT), Central Subfield Retinal Volume (CSRV), PED height, SRF volume, IRC volume, and the subfoveal choroidal thickness), as well as the presence or absence of qualitative parameters (IRC, intraretinal fluid, SRF, hemorrhage, dry retina, or other). The CRC will evaluate the images and the results of the CRC assessments will be transferred to the CRO responsible for data management.

The CSRT represents the average retinal thickness (µm) of the circular area within 1 mm diameter around the foveal center. The CSRV represent the total retinal volume (μm^3) of the circular area within 1mm around the foveal center. Both CSRT and CSRV are based on the automatically determined values from the dedicated SD/HD-OCT software. Before accepting the values provided by the dedicated SD/HD-OCT software, the OCT image acquisition technician must ensure adequate image quality for the assessment of the CSRT. Specifically the technician must exclude any artifacts of the automated segmentation. If artifacts are identified, a manual correction of segmentation lines must be done.

The SRT represents the retinal thickness (µm) measured at the focal center point (center of the anatomical fovea). It is determined on the single most central B-scan with the vitreo-retinal interface as the upper boundary and the lower border of band 4 (presumably RPE/Bruch's membrane) as the lower boundary.

The CRC will provide each site with a manual giving instructions and guidance on how to acquire, export and transfer OCT images. All investigational site personnel performing OCT assessments will be certified by the CRC prior to any study assessments taking place.

Historical OCT images for individual patients will also be evaluated by the CRC. Pseudo-anonymized historical retinal images (including one OCT volume scan acquired no greater than 28 days before the first IVT injection of aflibercept was administered to the study eye) will be collected and electronically transferred to the CRC. In addition, pseudo-anonymized historical retinal OCT images acquired after a minimum of 2 aflibercept injections indicating either no change or worsening disease activity (primary treatment failure subgroup) or an improvement in retinal morphology as defined by a reduction of ≥50µm in CSRT (suboptimal treatment response subgroup) will also be collected and transferred to the CRC. The data (i.e., copies of OCT images with relevant written Investigator interpretation) supporting these requirements should be recorded within the source documentation.

6.4.2 Color Fundus Photography, Fluorescein and Indocyanine Green Angiography

Fluorescein angiography (FA) is to be done in conjunction with color fundus photography (CF) at visits indicated in Table 6-1. Indocyanine green angiography (ICGA) is to be performed at Screening in all patients in order to determine eligibility for participation in the study. Imaging systems used in the study must be registered at the CRC, however individual certification by the CRC of site personnel to conduct FA, CF and ICGA imaging will not be required.

The Investigator will electronically send FA and CF images taken at Screening and Day 180, to the CRC. The ICGA images taken at Screening will also be transferred to the CRC. No print-outs will be accepted. [redacted] and presence/absence of PCV and RAP. The results of the CRC assessments will be transferred to the CRO responsible for data management.

The CRC will provide each site with a manual giving instructions and guidance on how to acquire and transfer FA, CF and ICGA images as applicable.

6.4.3 Fundus autofluorescence

Fundus autofluorescence (FAF) is to be done at visits indicated in Table 6-1. Imaging systems used in the study must be registered at the CRC and will include systems utilizing either confocal scanning laser ophthalmoscopy or fundus camera FAF. Individual certification by the CRC of site personnel to conduct FAF imaging will not be required.

The Investigator will electronically send FAF images taken at the Screening and Day 180 to the CRC. [redacted] As applicable, the CRC data will be used for the evaluation of the objectives having anatomical parameters as endpoints.

The CRC will provide each site with a manual giving instructions and guidance on how to take and transfer FAF images.

6.4.4 ETDRS Best-Corrected Visual Acuity

Best-corrected visual acuity (BCVA) will be assessed in the study eye (and separately in the fellow eye where indicated) in a sitting position using subjective refraction and ETDRS-like visual acuity testing charts at an initial testing distance of 4 meters.

If it is not possible to perform subjective refraction or visual acuity testing at 4 meters because visual acuity is too poor for the patient to read at least 4 letters on the refraction/visual acuity chart at this distance, the refraction/visual acuity testing should be attempted at 1 meter. Further details on refraction technique and visual acuity testing will be described in the BCVA testing manual which will be provided to the sites.

All investigational site personnel performing BCVA assessments will be certified prior to any study assessments taking place. The total BCVA score derived according to the BCVA testing manual captured in the BCVA Assessment Worksheet will be recorded in the eCRF.

6.4.5 Appropriateness of efficacy assessments

Evaluations described in this protocol are standard ophthalmic assessments in this indication and are required for a comparative evaluation of the results of this trial with the existing evidence from other trials.

6.5 Safety

Safety will be assessed by the type, frequency and severity of Adverse Events, ophthalmic examinations and vital signs. These assessments are performed according to the schedule in Table 6-1 and Table 6-2.

Significant findings that are present prior to signature of the informed consent must be included in the Relevant Medical History/Current Medical Conditions Screening page on the patient's eCRF. Significant findings that occur after the signature of the informed consent which meet the definition of an Adverse Event must be recorded as AEs in the patient's eCRF. These include significant findings identified by the CRC during the review of imaging data which will be communicated directly to Investigators.

All ocular assessments enabling identification of possible adverse events will be performed on both eyes.

6.5.1 Ophthalmic examinations

The standard ophthalmic examinations include slit lamp examination, anterior chamber examination, direct and indirect ophthalmoscopy of the macular and peripheral retina, and tonometry.

Slit lamp and fundus examinations will be performed prior to treatment with ranibizumab. In the study eye, tonometry is conducted at every study visit in both treatment groups to assess IOP, regardless of treatment administration afterwards. On visits when ranibizumab treatment is administered, post-injection tonometry may be performed as per Investigator discretion between 15 and 60 minutes after treatment in the study eye.

If study visit assessments and a corresponding treatment occur on separate days, a repeat ophthalmoscopy should be performed as safety check-up before treatment of the study eye. Results will be documented in the source documents but not in the eCRF. If any concern arises, treatment needs to be cancelled and a re-evaluation needs to take place.

6.5.2 Fellow eye

In order to characterize the patient and collect safety data, the assessment of BCVA will be performed in the fellow-eye (treated or not treated with ranibizumab) at Screening, Baseline (Day 1), Day 90 and Day 180. AEs and SAEs for the fellow eye will be recorded at every visit. Data will be recorded in the eCRF.

At the time when treatment of the fellow eye occurs, the BCVA assessment should be repeated prior to injection of ranibizumab and the data recorded in the eCRF.

6.5.3 Physical Examination

No physical examination will be performed.

6.5.4 Vital signs

At every study visit at least 3 separate measurements of the sitting blood pressure (systolic, diastolic) and pulse rate after at least 5 minutes rest, should be recorded in source documentation. At visits when ranibizumab treatment is administered, vital signs will be measured prior to the administration of ranibizumab.

The results from the final measurements of vital signs for each visit will be recorded in the eCRF.

6.5.5 Height and weight

Height (cm) and body weight (to the nearest kg, in indoor clothing but without shoes) will be measured at Screening. The results will be recorded in the eCRF.

6.5.6 Laboratory evaluations

No safety laboratory evaluations to assess blood or urine parameters will be performed with the exception of evaluation of pregnancy in women of child bearing potential as described in Section 6.5.8.

6.5.7 Electrocardiogram (ECG)

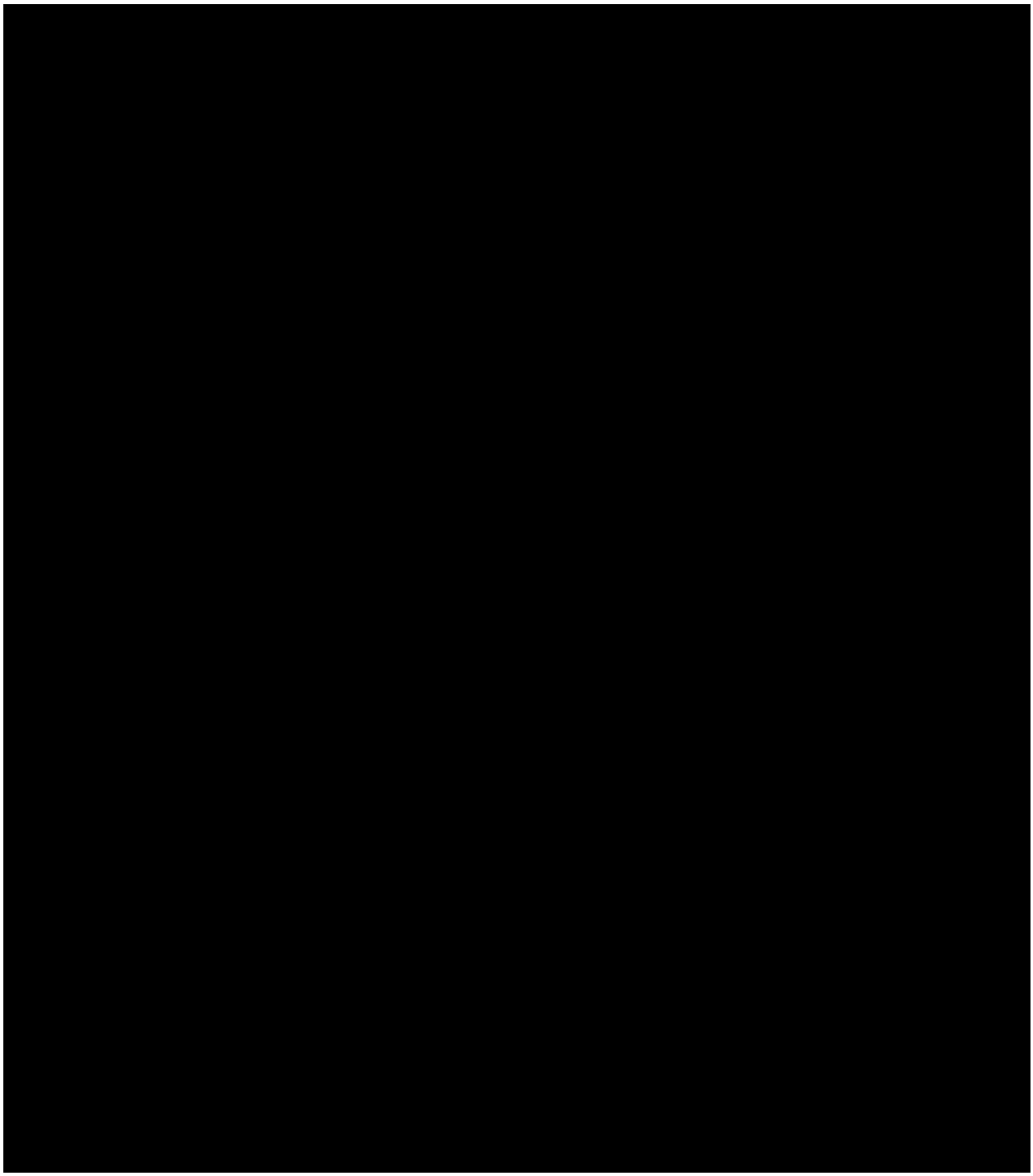
No ECG will be performed.

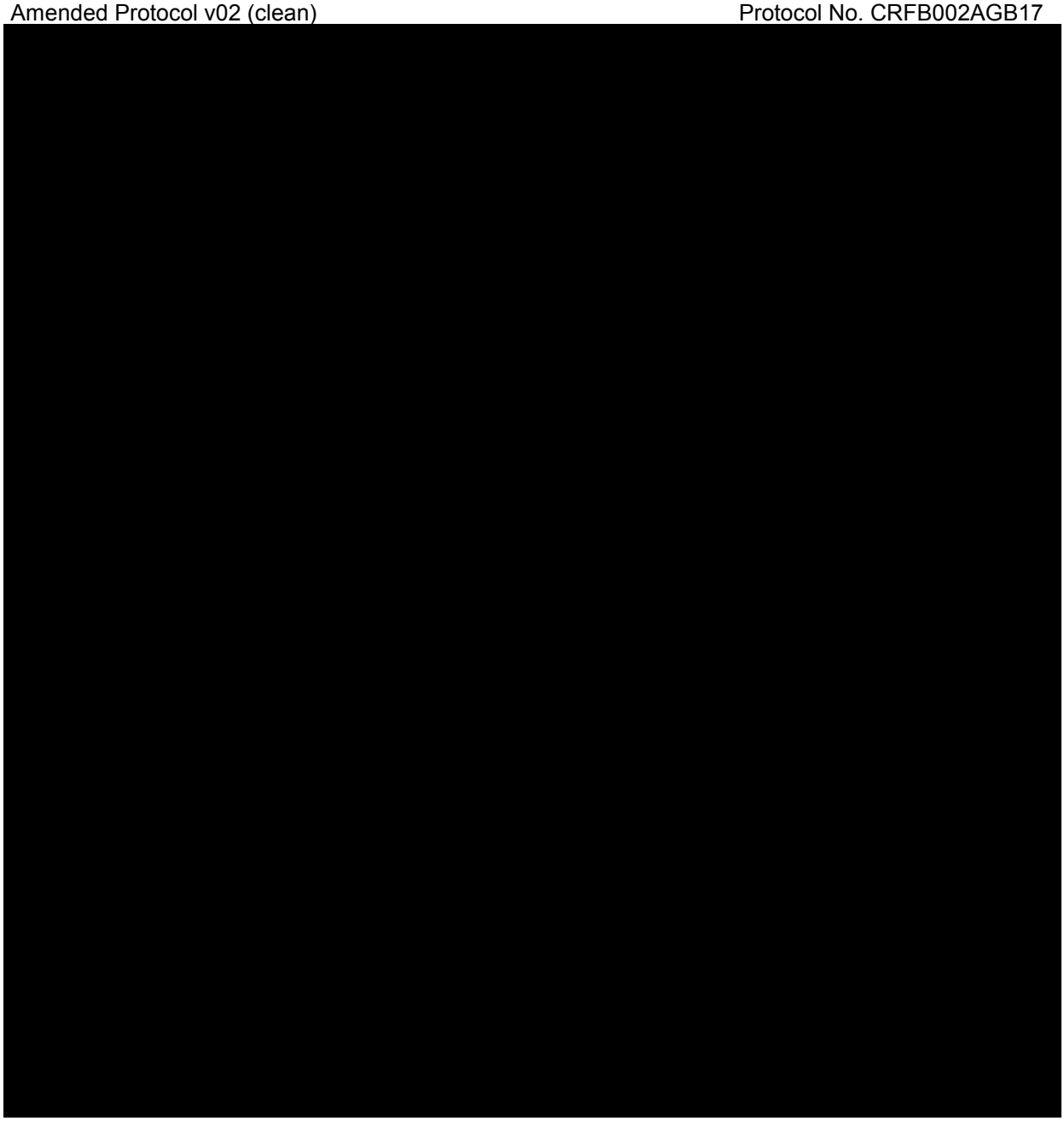
6.5.8 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test performed at Screening. A central laboratory approved by the Sponsor will be used for analysis of the serum. All results will be recorded in the eCRF. If positive, the patient must be discontinued from the study.

6.5.9 Appropriateness of safety measurements

The safety assessments selected for this study are standard for this indication and patient population.





7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. These include significant abnormal findings identified by the CRC during the review of imaging data which will be communicated directly to Investigators. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities
- its relationship to the study treatment (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE - See section 7.2 for definition of SAE)
- action taken regarding study treatment.
- Its site (non-ocular, left eye, right eye, both eyes).

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 treatment temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given

- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the IB or local labelling/package insert. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The Investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the Investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- 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 nAMD, 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 signing the informed consent
  - 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.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the eCRF, SAEs also require individual reporting to DS&E as per section 7.2.2.

7.2.2 SAE 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.

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 (*either initial or follow up information)* is collected and recorded on the paper Serious Adverse Event Report Form. The Investigator must assess the relationship of any SAE to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, 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. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the IB or local labelling/package insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and 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 investigational treatment 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.

7.3 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment 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.

Pregnancy should be recorded on the Pharmacovigilance Pregnancy Form and reported by the Investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Novartis representative will review the protocol and eCRFs with the Investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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 eCRFs 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 eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated Investigator staff will enter the data required by the protocol into the eCRF using fully validated software that conforms to US CFR 21Part 11 requirements. Designated Investigator site staff will not be given access to the eCRF system until they have been trained. Automatic and manual validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the eCRF are complete and accurate. After database lock, the Investigator will receive copies of the patient data from the CRO for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff and staff at a CRO working on behalf of Novartis will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated Investigator site staff are required to respond to the query and confirm or correct the data. All relevant comments should be added to the eCRF using the Investigator Comment feature.

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

Data about the study drug dispensed to the patient will be tracked using the eCRF. The eCRF system will be supplied by a CRO, who will also manage the database.

OCT, color fundus photographs, fluorescein angiograms, ICGA and fundus autofluorescence images will be processed centrally by the CRC and the results will be sent electronically to a designated CRO for incorporation into the master database. Data management staff will perform a reconciliation of the data entered into the eCRF versus what is received from the CRC. At a minimum, this reconciliation will include header reconciliation, visit window checks, duplicate record checks, out-of-range checks as defined by the Clinical Trial Team and checks to address missing reading center data.

[redacted]

At the conclusion of the study, the occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. Following database lock, the database will be sent electronically to Novartis (or a designated CRO). Any changes to the database after that time can only be made by joint written agreement by the Clinical Trial Leader, the Trial Statistician, the Data Manager and the Quality Manager.

8.4 Data Monitoring Committee

Not applicable.

8.5 Adjudication Committee

Not applicable

9 Data analysis

The statistical analysis will be performed by staff at a CRO working on behalf of Novartis.

There will be one interim analysis after the first 50 patients have completed all visits up to Day 90 (see section 9.6) and the final analysis after all patients have completed the study.

Descriptive statistics include n (the number of non-missing values), mean, standard deviation, median, minimum, maximum and, where appropriate, confidence intervals for continuous variables and frequencies and percentages for categorical variables and will be provided where applicable for patients and study eye. All data will be listed by patient, and where applicable, by eye.

For statistical purposes, baseline will be defined as the last available non-missing value collected just prior to the start of treatment in the study eye.

For patients with screening assessments who do not enter the treatment period, data will only be listed. For patients who do not enter the treatment period due to a study eye specific exclusion criterion, descriptive statistics as described above will be provided.

Unless otherwise specified, all statistical tests will be two-sided and use the 0.05 level of significance.

Further technical details and discussion of the following statistical considerations will appear in the Statistical Analysis Plan, which will be finalized prior to database lock and the analysis.

9.1 Analysis sets

For all patients only one eye will be considered as the study eye, but efficacy and safety parameters will be recorded for both eyes. In the event that a subject develops visual impairment due to nAMD in the fellow eye (non-study eye) during the study which is treated at the Investigator's discretion according to the standard of care, any additional data (except for BCVA, ranibizumab injections and AEs and SAEs that occur in the fellow eye) collected according to routine practice will not be recorded on the eCRF. Data presentations will distinguish study and fellow eye values.

The **Full Analysis Set (FAS)** will consist of all patients who received at least one application of study treatment in the study eye, have baseline and have at least one post-baseline assessment for CSRT. Following the intent-to-treat principle, patients will be analyzed according to the treatment assigned. No data will be excluded from the FAS analyses because of protocol deviations.

The **Per Protocol Set (PPS)** will consist of all patients in the FAS who followed the assigned treatment and completed the study without clinically significant protocol deviations. Clinically significant protocol deviations will be defined in the Statistical Analysis Plan. If deviations do occur, then the data from specific patients, visits, or evaluations may be excluded from the PPS. The criteria and determination of clinically relevant protocol deviations and patient specific identification of data to be excluded from the PPS will be databased and finalized prior to database lock.

The **Safety Set (SAF)** will consist of all patients who received at least one application of study treatment in the study eye and had at least one post-baseline safety assessment. The statement that a patient had no adverse events also constitutes a safety assessment.

All efficacy evaluations will be carried out on the Full Analysis Set and all safety evaluations will be carried out on the Safety Set.

For sensitivity purposes, the primary analysis will be repeated using the Per Protocol Set. Any major discrepancies in the results across analyses will be investigated as necessary.

Defined subgroups

Two subgroups of the FAS are defined for exploratory analyses (see section 4.1 for full definitions):

1) Group 1. Primary treatment failure (PTF)
2) Group 2. Suboptimal treatment response (STR)

Analyses to be presented for subgroups in addition to the main analysis sets (FAS or SAF) are indicated below.

9.2 Patient demographics and other baseline characteristics

Descriptive statistics will be provided for patient demographics and all baseline characteristics (including the baseline values of the main 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. Data will be summarized for the FAS and also for the subgroups PTF and STR.

9.3 Treatments

Study treatment

Descriptive statistics will be provided for exposure to study treatment using the Safety Set, PTF and STR subgroups. The number of ranibizumab injections will be presented by visit and cumulatively. Summaries will be presented for the injections in the study eye and the fellow treated eye as appropriate. Other data related to the application procedure will be summarized as appropriate.

The proportion of patients who received bilateral injections of ranibizumab (both the study eye and fellow eye injected at the same visit) will be summarized by visit.

Analyses of the treatment exposure will include:

- Treatment frequency (total number of injections and number of injections by visit)
- Reason for PRN treatment (patient symptoms, BCVA decline, or OCT criteria)
- Compliance to treatment regimen (if treatment given monthly per protocol or as a response to changes in patient symptoms, BCVA or OCT)

Reasons for discontinuation from the study will be summarized.

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.

9.4 Analysis of the primary variable(s)

The primary objective is to demonstrate that the mean change from baseline in CSRT (as determined by OCT) at Day 90 is less than zero.

9.4.1 Variable(s)

The primary variable will be the difference from baseline to Day 90 in CSRT.

9.4.3 Handling of missing values/censoring/discontinuations

In the event that CSRT is missing for Day 90, the analysis will follow an LOCF (Last Observation Carried Forward) approach for the Full Analysis Set. This will only be done for the primary outcome.

9.4.4 Supportive analyses

For sensitivity purposes, the primary analysis will be repeated using the PPS. Any major discrepancies in the results across analyses will be investigated as necessary. For the PPS, it is assumed that a complete set of valid observations for the efficacy endpoints will be available. Therefore, no general rules for handling of missing values are specified. In case missing values occur, details regarding their handling will be described in a Statistical Analysis Plan.

9.5 Analysis of secondary variables

9.5.1 Efficacy variable

Secondary variables are:

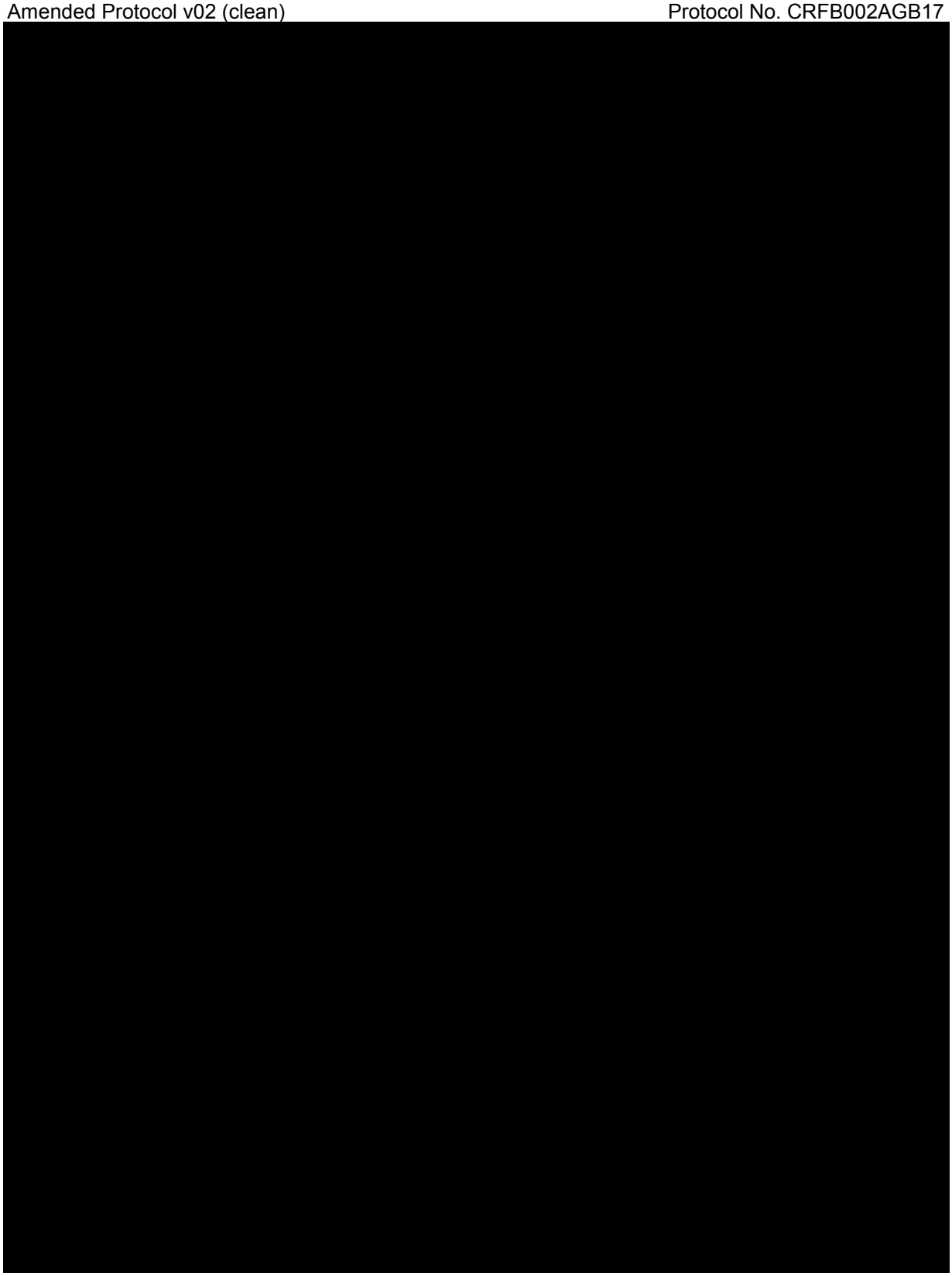
From Optical Coherence Tomography (OCT):

- Mean change from baseline to visits up to Day 180 in Subfoveal Retinal Thickness (SRT), Central Subfield Retinal Thickness (CSRT), and Central Subfield Retinal Volume (CSRV).
- Presence or absence of qualitative OCT parameters (intra-retinal cystoid changes (IRCs), subretinal fluid (SF), pigment epithelial detachments (PEDs), or dry retina).
- Mean change from baseline to visits up to Day 180 in PED height, SF volume, and IRC volume.

From visual acuity:

- Mean change in best corrected visual acuity (BCVA) from Baseline to visits up to Day 180.
- Mean change in BCVA from Day 90 to Day 180.
- Proportions of patients gaining ≥5, ≥10 and ≥15 ETDRS letters from Baseline at visits up to Day 180.
- Proportion maintaining vision (<15 ETDRS letters lost from baseline) at visits up to Day 180.

The analysis of the secondary efficacy objectives will focus on the FAS. At all time-points assessed, each efficacy variable will be presented graphically and descriptive statistics provided based on absolute values and changes from baseline.



9.5.2 Safety variables

Safety parameters will include adverse events, the results of ophthalmic examinations, intraocular pressure (IOP), vital signs, and laboratory results if reported as AE.

All safety analyses will be performed using the Safety Set.

Adverse Events

Adverse events will be deemed treatment emergent if the onset date is on or after the date of first study treatment. Any adverse events recorded prior to the start of study treatment will be listed as prior medical conditions. Only treatment-emergent adverse events will be summarized.

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

All the ocular AEs after the first treatment of the fellow eye will be listed according to whether they occurred in the study eye or fellow treated eye.

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 adverse events suspected to be treatment related.

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

Vital signs and special tests

Vital signs will be summarized by presenting shift tables using clinically notable abnormal ranges with thresholds representing clinical relevant abnormality and by presenting descriptive statistics of raw data and change from Baseline. Values outside the clinically notable range will be listed by patient and treatment group and flagged in data listings. IOP measurements will be presented descriptively (absolute values and change from baseline).

9.6 Interim analyses

An interim analysis will be conducted after the first 50 patients have completed visits up to Day 90. This will be used primarily to provide preliminary data on the safety of ranibizumab in patients with nAMD with either primary treatment failure or suboptimal treatment response to aflibercept. Descriptive analyses will be carried out on the main safety and efficacy variables. The results from this Day 90 analysis will be submitted for publication. As no hypothesis tests will be carried out, no statistical adjustments are required.

10 Ethical considerations

10.1 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 CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. 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. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Novartis before submission to the IEC, and a copy of the approved version must be provided to the Novartis monitor after IEC approval.

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional IEC approval will be obtained.

10.3 Responsibilities of the Investigator and the IEC

Before initiating a trial, the Investigator/institution should obtain approval/favorable opinion Independent Ethics Committee (IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. 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 Quality Assurance representatives, designated agents of Novartis, 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.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. Efficacy and safety data will be presented at both national and international scientific meetings. In addition, upon study completion and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results. Future authorship will be determined according to published ICMJE criteria (http://www.icmje.org/).

11 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 requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances should an Investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an 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 and health authorities, where required, it cannot be implemented. All significant protocol deviations will be recorded and reported in the clinical study report.

11.1 Protocol Amendments

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 IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IEC is notified.

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, the reporting requirements identified in section 7 Safety Monitoring should be followed.

12 References

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13 Appendix 1: Clinically notable laboratory values and vital signs

The criteria for clinically notable abnormal vital signs are shown in. In order to be identified as being potentially clinically notable abnormal, an on-treatment vital sign value would need to meet the criterion value, and represent a change of at least the magnitude noted in the critical values column.

Table 13-1 Clinically notable abnormal vital signs

Variable	Type of abnormality	Critical value
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
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