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Clinical Development

RFB002/ranibizumab

Clinical Trial Protocol CRFB002AAU17

Development of new geographic atrophy in patients with neovascular (wet) age-related macular degeneration: a comparison of ranibizumab and aflibercept.

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List of abbreviations

AE	Adverse event
AMD	Age-related macular degeneration
BCVA	Best-corrected visual acuity
BRB	Blood retinal barrier
BRVO	Branch retinal vein occlusion
CF	Colour fundus photography
CFR	Code of Federal Regulations
CMH	Cochran-Mantel-Haenszel
CNV	Choroidal neovascularisation
CRC	Central reading centre
CRO	Contract Research Organisation
CRVO	Central retinal vein occlusion
CRT	Central retinal thickness
CS	Contrast sensitivity
CSFT	Central subfield thickness
CSFV	Central subfield volume
CSR	Clinical Study Report
DME	Diabetic macular edema
DS&E	Drug Safety and Epidemiology
eCRF	electronic Case Report Form
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
EU SmPC	European Union summary of product characteristics
FA	Fluorescein angiography
FAS	Full Analysis Set
FAZ	Foveal avascular zone
GCP	Good Clinical Practice
GA	Geographic Atrophy
IB	Investigator’s brochure
ICG	Indocyanine Green [angiography]

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent ethics committee
IOP	Intraocular pressure
IRB	Institutional review board
IRF	Intraretinal Fluid
IS	Inner Segment
IUD	Intrauterine device
IUS	Intrauterine system
IWRS	Interactive Web Response System
LOCF	Last observation carried forward
logMAR	Logarithm of the minimum angle of resolution
MacTSQ	Macular Disease Treatment Satisfaction Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
NEI-VFQ-25	National Eye Institute Visual Function Questionnaire-25
OCT	Optical coherence tomography
OS	Outer segment
PCV	Polypoidal choroidal vasculopathy
PPS	Per Protocol Set
PRN	Pro re nata, as required
RMP	Risk Management Plan
RPE	Retinal Pigment Epithelium
RVO	Retinal vein occlusion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD/HD-OCT	Spectral domain/ high-definition optical coherence tomography
SDV	Source Document Verification
SRF	Subretinal Fluid
TD-OCT	Time domain optical coherence tomography
VA	Visual acuity
VEGF	Vascular endothelial growth factor
wAMD	Neovascular (wet) age-related macular degeneration
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrolment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	The planned stage of the subjects' participation in the study. Each epoch serves a purpose in the study as a whole. Typical epochs are: determination of subject eligibility, wash-out of previous treatments, exposure of subject to treatment or to follow-up on subjects after treatment has ended
Fellow eye	The contralateral eye to the study eye which may either be treated prior to patient entering the study (named first eye/non-study) or treated subsequent to the patient entering the study (second eye/non-study)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product"
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. Investigational treatment generally *does not include* other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Masking	A term that is interchangeable with the term "blinding" but is more typically used in studies relating to visual loss
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Subject Number	A number assigned to each patient who enrols into the study
Part	A subdivision of a single protocol into major design components. These parts often are independent of each other and have different populations or objectives. For example, a single dose design, a multiple dose design that are combined into one protocol, or the same design with different patient populations in each part
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
Randomisation number	A unique identifier assigned to each randomised patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Amendment 2 – 19 Jan 2015

Amendment rationale

A protocol amendment was released on 19 January 2015 pertaining to specific sections of the protocol as shown in the track change version of the protocol using ~~strike through red font~~ for deletions and red underlined for insertions.

The major changes made to the protocol are summarised in this section. Other minor administrative changes are incorporated directly into the protocol. The major changes include the following:

- Change to primary endpoint: The Steering Committee agreed a continuous variable is a more valid way to assess Geographic Atrophy than a dichotomous variable, as a dichotomous variable would miss patients with clinically significant Geographic Atrophy that it is considered under the 250µm definition cutoff (There is no uniformity in the cutoff point with 175µm also commonly used). For example a patient with no Geographic Atrophy at baseline but 240µm at year 2 would be considered to have no Geographic Atrophy for the whole study. However a patient with 230µm at baseline and 260µm at year 2 would be considered to have had a significant increase in Geographic Atrophy under a dichotomous assessment. This change to the primary endpoint will also align with two ongoing landmark Geographic Atrophy studies underway, the CHROMA (NCT02247479) and SPECTRI (NCT02247531) studies sponsored by Hoffmann-La Roche. Modifying the primary endpoint for CRFB002AAU17 will allow a larger pool of trials and evidence reporting with a common endpoint. The subsequent change in statistical analysis and modelling reflects the change from a dichotomous primary endpoint to a continuous variable.
- A change in the 12 and 24 month visit window from +/- 14 days to +/-6 days to reduce the possibility of the key secondary endpoint of injection number being biased by the decision of the unmasked investigator deciding to combine a variable visit and 12 or 24 month assessment visit.
- The addition of enhanced depth imaging to Table 6-1- Assessment schedule. This is a specific OCT technique to image the deeper layers of the eye. It is already in the Central Reading Centre manual but to maximize collection of this data it is added as a reminder within the protocol.
- The addition of text ‘week 8’ to section 6.4.1, to align with the assessment schedule table 6-1,
- Formal allowance of the use of the ranibizumab pre-filled syringe.
- Update of patient discontinuation criteria to the updated International Vitreomacular Traction Study (IVTS) Group Classification 2013 for Macular Holes nomenclature.

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

The changes herein do not affect the Informed Consent, sites are not required to update the patient Informed Consent that is currently in use.

Amendment 1 – 12 December 2013

Amendment rationale

A protocol amendment was released on 12th December 2013 pertaining to specific sections of the protocol as shown in the track change version of the protocol using ~~strike through red font~~ for deletions and red underlined for insertions.

The major changes made to the protocol are summarised in this section. Other minor administrative changes are incorporated directly into the protocol. The major changes include the following:

- For the VEGF sampling the wording 'Serum' is replaced with 'Plasma' VEGF.
- Inclusion of AutoFluoresence image at Week 4 and Week 8 to make allowance for the first image to be obstructed by haemorrhage. The CRC may use the clearest of the 3 initial readings as the baseline image.
- Optional test for Colour Fundus Photography at all visits if there is presence of haemorrhage so it may be confirmed by the blinded CRC.
- Inclusion of prohibited treatments to exclusion criteria 19-20 as per existing table 5-1 Prohibited Medications
- Exclusion criterion of patients with total non contiguous area of Geographic Atrophy is amended to patients with one or more patches ≥ 250µm of Geographic Atrophy in either eye. This change is based on the recent CATT publication (Grunwald 2014) to minimise any bias of pre-existing Geographic Atrophy on the primary end point.
- Additional angiographic assessment at week 8 to allow for obstruction of the first image by haemorrhage. The CRC may use the clearer of the 2 initial readings as the baseline image.
- Removal of pseudoexfoliation as an exclusion criterion to bring in line with clinical practice. There is no safety or data quality reason to exclude these patients from the trial.
- Allowance of 3 failed extensions before the break point treatment interval is set for the rest of the study, which brings the protocol in line with clinical practice. This allows subjects not to be unnecessarily restricted to 4 weekly treatments for the two year study period, if they were to fail the first two extensions.
- Removal of Data Monitoring Committee as this will not be required for this study based on the recent VIEW 96 weeks (Schmidt-Erfurth 2014) publication which found no significant differences in safety or efficacy when both were used on a PRN regimen.

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

In addition, as the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Protocol synopsis

Protocol number	CRFB002AAU17
Title	Development of new geographic atrophy in patients with neovascular (wet) age-related macular degeneration: a comparison of ranibizumab and aflibercept
Brief title	Geographic atrophy: a comparison of ranibizumab and aflibercept
Sponsor and Clinical Phase	Novartis Pharmaceuticals Australia Pty Ltd. Phase IV
Investigation type	Drug
Study type	Interventional
Purpose and rationale	With the increasing use of targeted anti-VEGF therapies for the treatment of age-related macular degeneration (AMD), there has been a rising concern related to the risk of progression of geographic atrophy with intensive and long term use of these agents. The association is thought to stem from the prolonged inhibition of VEGF-A, which is known to act as a vascular survival factor in the adult eye (Hoffman et al, 2000), and VEGF-B, which is known to confer neuroprotective properties in the eye (Zhang et al, 2009; Dhondt et al, 2011). The two most commonly used anti-VEGF therapies for the treatment of wet AMD, ranibizumab and aflibercept, have differing mechanisms of action in terms of their receptor inhibition profiles. These different biologic characteristics may have varying clinical consequences in terms of the risk of progression of geographic atrophy within the retina. Ranibizumab is a recombinant, humanised, monoclonal antibody that neutralises all forms of VEGF-A, while aflibercept is a recombinant fusion protein which neutralises all VEGF-A isoforms, VEGF-B and placental growth factor (PlGF). Aflibercept by its ability to inhibit VEGF-B (in addition to VEGF-A and PlGF) may confer a greater risk for the development of geographic atrophy in patients. The aim of the present study is to compare the development of new geographic atrophy in patients treated with 0.5 mg ranibizumab “inject and extend” versus those treated with 2.0 mg aflibercept “inject and extend” over 24 months.

Primary Objective(s) and Key Secondary Objectives	The primary objective for the study will be the mean change in area of geographic atrophy in the study eye from baseline to month 24 as measured by multimodal imaging assessed by an independent reading centre masked (blinded) to the treatment arms. Key secondary objectives include assessment of: • the number of injections from baseline to month 12 • the mean change in BCVA (logMAR) from baseline to month 12
Secondary Objectives	Secondary objectives will include: • the mean change in area of existing and newly developed geographic atrophy from baseline to month 12 • the proportion of patients showing geographic atrophy from baseline to month 12 • the number of injections from baseline to month 24 • the mean change in BCVA (logMAR) from baseline to month 24 • the mean change in central retinal thickness (CRT) from baseline to months 12 and 24 • the proportion of patients showing no intraretinal fluid (IRF) and subretinal fluid (SRF) at months 2, 12 and 24 • the proportion of patients showing greater than and equal to a 15 letters (logMAR) gain from baseline to months 12 and 24 • the proportion of patients showing less than and equal to a 15 letters (logMAR) loss from baseline to months 12 and 24 • the number of times a patient needed to return to monthly treatments during the 24 months • retinal nerve fibre analysis at baseline and month 24 • the concentration of plasma VEGF at baseline and 7 days post-injection following Week 4 and Week 8 mandated intravitreal injections in full population and treatment naïve patients • ocular and systemic adverse events at all visits • ocular inflammation at baseline and 7 days post-injection following 3rd mandated intravitreal injection
Study design	This is a phase IV, randomised, controlled, masked study recruiting patients with one treatment-naïve eye presenting with subfoveal choroidal neovascularisation (CNV) secondary to wet AMD. At screening, following the informed consent process, patients will be assessed for study eligibility by assessment of visual acuity using logarithm of the minimum angle of resolution (logMAR), stereoscopic biomicroscopic slit-lamp fundus examination (78 D or similar lens); fluorescein angiogram (FA); colour fundus photography; fundus autofluorescence and optical coherence tomography (OCT). Eligible patients will be enrolled and then randomised to one of two arms: Arm 1: 0.5 mg ranibizumab using an inject and extend regimen

	Arm 2: 2.0 mg aflibercept using an inject and extend regimen Since the study will recruit patients who are either treatment-naïve in both eyes or, alternatively, treatment naïve in only one eye (i.e. the first/fellow [non-study] eye may be treated with any anti-VEGF), the patients will be stratified at randomisation to ensure an even distribution across the two study groups to account for any potential contralateral effect of the first/fellow eye medication on the study eye. Randomisation will occur within three strata: two treatment naïve eyes, one eye (first/fellow non-study eye) being treated with ranibizumab, and one eye (first/fellow non-study eye) being treated with an anti-VEGF other than ranibizumab.
Population	This will be a multi-centre study conducted in approximately 21 sites across Australia and New Zealand. Each site will recruit approximately 15 patients. A total of approximately 278 patients will be recruited to this study, with approximately 139 randomised to each study arm. This accounts for an expected 15% drop out rate over 24 months. Assuming an average 20% screen failure rate, approximately 333 patients will need to be screened to have approximately 278 patients found eligible and commencing treatment in the trial.
Inclusion criteria	*Inclusion criteria for patient:* 1. Written informed consent must be obtained before any study-related assessment is performed. 2. Male or female patients ≥50 years of age. *Inclusion criteria for study eye:* 3. Diagnosis of active subfoveal CNV secondary to wet AMD without restriction of lesion size, with visual impairment being exclusively due to an active wet AMD lesion. Active lesions will be characterised by any of the following: abnormal retinal thickness, with evidence of intraretinal, subretinal or sub-pigment epithelial fluid accumulation, confirmed by OCT; presence of intraretinal or subretinal haemorrhage; leakage shown on a FA unless solely due to dry, fibrotic staining; visual acuity deterioration considered likely to represent CNV. 4. BCVA score at both Screening and Baseline must be 23 letters or more as measured by the 3 metre Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts, inclusively (or approximate Snellen equivalent to 3/60+3). If both eyes are eligible at Screening and Baseline, the investigator will decide the study eye based on clinical judgment. Only one eye needs to meet the study entry criteria.
Exclusion criteria	Patients fulfilling any of the following criteria are not eligible for inclusion in this study. *Exclusion criteria for patient:* 1. Inability to comply with study or follow-up procedures. 2. Pregnant or nursing (lactating) women. 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 sterilisation (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 sterilisation (at least 6 m prior to screening). For female subjects on the study, the vasectomised 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. 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. 5. Stroke or myocardial infarction less than 3 months prior to Screening. 6. Uncontrolled blood pressure defined as systolic value of >160 mm Hg or diastolic value of >100 mm Hg at Screening or Baseline. 7. Known hypersensitivity to ranibizumab or aflibercept or any component of the ranibizumab or aflibercept formulation, or fluorescein. *Exclusion criteria for ocular medical history and conditions:* *For both eyes:* 8. Any active periocular or ocular infection or inflammation (e.g., blepharitis, conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) at the time of Screening or Baseline. 9. 1 or more patches of geographic atrophy $\geq$ 250µm in longest linear dimension.

	10. Uncontrolled glaucoma (intraocular pressure [IOP] ≥30 mm Hg on medication or according to investigator's judgment) at the time of Screening or Baseline. 11. Neovascularisation of the iris or neovascular glaucoma at the time of Screening or Baseline. 12. Inability of obtaining multimodal images of sufficient quality to be analysed. *For study eye:* 13. Visually significant cataract (likely to require surgery within the next 12 months), aphakia, severe vitreous haemorrhage, rhegmatogenous retinal detachment, proliferative diabetic retinopathy or CNV of any cause other than wet AMD (e.g., ocular histoplasmosis, pathologic myopia macular hole) at the time of Screening and Baseline. 14. Structural damage within 0.5 disc diameter of the centre of the macula (e.g., vitreomacular traction, epiretinal membrane, scar, laser burn, foveal atrophy) at the time of screening that in the investigator's opinion could preclude visual function improvement with treatment. *Exclusion criteria for prior or current systemic medication:* 15. Use of other investigational drugs within 30 days or 5 half-lives from baseline, whichever is longer. 16. Current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve as outlined in the Lucentis and Eylea Product Information. *Exclusion criteria for prior or current ocular treatment:* *For study eye:* 17. Treatment with any anti-angiogenic drugs (including any anti-VEGF agents) prior to Baseline in eye. 18. Any intraocular procedure (including Yttrium-Aluminium-Garnet capsulotomy) within 2 months prior to Baseline or anticipated within the next 6 months following Baseline. *Exclusion criteria of prohibited treatments (study eye):* 19. Intra or periocular corticosteroids (including sub tenon but excluding topical formulations) 20. Intraocular corticosteroid implants *PLEASE NOTE REGARDING TREATMENT FOR FELLOW EYE:* Treatment with any anti-angiogenic drug (including any anti-VEGF agents) is allowed prior to Baseline in fellow eye.
Investigational therapies	Aflibercept 2.0mg intraocular injections. Ranibizumab 0.5mg intraocular injections.

Efficacy assessments	• Ophthalmic examination • Colour fundus photography and fluorescein angiography • BCVA measured by logMAR • Autofluorescence • Optical Coherence Tomography
Safety assessments	The safety assessments selected for this study are standard for the indication and patient population and will include the results of ophthalmic examinations, IOP, vital signs, and laboratory results if reported as an adverse event. In addition, systemic adverse events at all visits and ocular inflammation at baseline and 7 days post-injection following 3rd mandated intravitreal injection will be assessed.
Other assessments	• Vital signs • Serum pregnancy test • Plasma VEGF
Data analysis	The primary objective of this study is to compare the risk of the study eye developing new geographic atrophy after receiving either 0.5 mg ranibizumab or 2.0 mg aflibercept. The primary endpoint is the mean change in area of geographic atrophy in the study eye from baseline to month 24. Key secondary endpoints are the number of injections from baseline to month 12 and the mean change in BCVA from baseline to month 12. These will be analysed ahead of the primary endpoint when 12 month data are available to explore the inject and extend treatment algorithm for anti-VEGF therapy described specifically in this study since it represents a novel approach to patient management not previously explored in a randomised, controlled trial as an alternative to monthly or prn regimens. The primary endpoint and all of the secondary endpoints will be analysed and requested at the end of the study. The primary analysis will be performed on the Full Analysis Set fitting a mixed model. The number of injections will be analysed using Poisson or negative binomial regression. BCVA will be analysed using a mixed model approach. This approach takes into account the repeated measures nature of the data; it allows all results to be included and does not require imputation of missing data if the missing observations can be assumed to be missing at random. Other secondary endpoints that will be analysed using the mixed model approach include mean change in area of new and existing geographic atrophy at 12 and 24 months, mean change in BCVA at 24 months, mean change in CRT. Secondary endpoints of resolution of intraretinal fluid (IRF) and subretinal fluid (SRF), the achievement of at least a 15 letter improvement and less than a 15 letter loss will be analysed using logistic regression. Descriptive statistics such as n, mean, standard deviation, minimum and maximum will be provided by treatment and visit for all continuous endpoints and n and percent for categorical endpoints.
Key words	Age-related macular degeneration, ranibizumab, aflibercept, geographic atrophy, inject and extend

1 Introduction

1.1 Background

Age-related macular degeneration (AMD) is the leading cause of severe loss of vision in the elderly population. Genetic, environmental and health factors play an important role in the pathogenesis of the disease. Among the clinical features, the cumulative deposition of acellular, polymorphous debris between the retinal pigment epithelium and Bruch's membrane, known as drusen, at the central region of the macula is considered a main predictor of the establishment of a progressive and degenerative process, in which an advanced AMD, defined as the presence of choroidal neovascularisation (CNV) and/or geographic atrophy, can be the final result.

In recent years, the earlier diagnosis, precise and close monitoring of patients with neovascular (wet) age-related macular degeneration (wAMD), in association with efficacious medications with a well-characterised safety profile such as ranibizumab, have contributed to a decrease of cases of blindness as well as improved quality of life of the patients with this chorioretinal degenerative disease.

1.2 Purpose

The advent of intravitreal anti-vascular endothelial factors (anti-VEGF) has revolutionised the treatment of neovascular age-related macular degeneration (AMD). The first of these therapies to be registered and reimbursed in Australia, ranibizumab is a recombinant, humanised, monoclonal antibody that neutralises all forms of VEGF-A, a key mediator of the neovascular process in AMD. While the pivotal phase III trials for ranibizumab, ANCHOR and MARINA, demonstrated previously unseen increases in visual acuity with a monthly dosing regimen (Rosenfeld et al, 2006; Brown et al, 2009), subsequent clinical trials demonstrated that similar visual outcomes could be achieved with less than monthly dosing. Two such studies, in which a ranibizumab prn arm was incorporated, were the CATT and HARBOR studies (Martin et al, 2012; Busbee et al, 2013). Patients in CATT treated with 0.5 mg ranibizumab prn experienced a 6.8 letter gain in visual acuity with 6.9 injections by 12 months. Similarly, patients in HARBOR treated with 0.5 mg ranibizumab prn experienced an 8.2 letter gain in visual acuity with 7.7 injections by 12 months. These injection frequencies are comparable to that cited in the Pharmaceutical Benefit Advisory Committee (PBS) Drug Utilisation Sub-Committee (DUSC) report which stated that, in real clinical practice, Australian patients are receiving an average of 7.42 injections in the first year of treatment.

The second of the wet AMD therapies to be registered and reimbursed in Australia, aflibercept, is a recombinant fusion protein which neutralizes all VEGF-A isoforms, VEGF-B and placental growth factor (PlGF). The pivotal phase III trials for aflibercept, the VIEW I and VIEW II studies, demonstrated that the 2 mg dose administered for three consecutive months followed by 8 weekly injections thereafter was non-inferior to monthly 0.5 mg ranibizumab in terms of visual acuity benefit by 12 months (Heier et al, 2012).

The injection of anti-VEGF medications into the vitreous cavity has the potential for both ocular adverse events (such as endophthalmitis, lens trauma and retinal detachment) and systemic adverse events (arterial thromboembolic events including myocardial infarction, cerebrovascular events and death). Thus limiting the number of injections is desirable if the same visual acuity result can be achieved. An additional consequence of greater injection frequency is the potential for progression of geographic atrophy, which has been hypothesised as being exacerbated over time with intensive, long-term anti-VEGF therapy.

VEGF-A is known to act as a vascular survival factor in the adult eye and has been suggested to be involved in the paracrine signalling between the RPE and choriocapillaris (Hoffman et al, 2000). This is consistent with findings that VEGF-A (121) and VEGF-A (165) isoforms are most abundantly expressed in the choroid, RPE, retina and iris tissue (Bhisitkul et al, 2006). Studies have shown that inactivation of VEGF-A in the RPE (in VEGF-/- knockout mice) results in RPE degeneration and, specifically, that the absence of the diffusible VEGF-A isoforms 120 and 164 leads to an age-dependent degeneration of the RPE-CC that is similar in many respects to dry/atrophic AMD. RPE loss, choroidal remodelling, and increased photoreceptor apoptosis lead to a decline in visual acuity as detected by ERG (Saint-Geniez *et al*, 2009). In the CATT study, the development of geographic atrophy was more common in eyes receiving a greater number of injections by 2 years, i.e. 25.8% of eyes treated with monthly ranibizumab and 17.9% of eyes treated with monthly bevacizumab compared to 15.2% treated with ranibizumab prn and 12.9% treated with bevacizumab prn. By correlation, the patient groups treated with more injections of either ranibizumab or bevacizumab showed a greater reduction in presence of fluid compared to those patient groups in which a prn regimen was used (Martin et al, 2012). Therefore, one possible consequence of prolonged VEGF-A inhibition in the eye, as observed with monthly dosing, is an increased risk of geographic atrophy.

VEGF-B, which is inhibited by aflibercept but not ranibizumab, is known to confer neuroprotective properties in the eye. It has been shown to be involved in retinal recovery processes and plays a potent role of neuroprotection in mouse retinal ganglion cells after optic nerve crush (Zhang et al, 2009). Studies in VEGF-B-deficient mice suggest that VEGF-B, instead of acting as an angiogenic factor, exerts direct neuroprotective effects through its neuronal receptor FLT1 (Dhondt et al, 2011). Therefore again, one possible consequence of VEGF-B inhibition in the eye is an increased risk of geographic atrophy. Indeed, aflibercept by its ability to inhibit VEGF-B (in addition to VEGF-A and PlGF) may confer a greater risk for the development of geographic atrophy in patients.

The aim of the present study is to compare the rate of progression of geographic atrophy in the study eye of patients treated with 0.5 mg ranibizumab “inject and extend” versus those treated with 2.0 mg aflibercept “inject and extend” over 24 months. The primary objective for the study will be the mean change in area of geographic atrophy in the study eye from baseline to month 24 as measured by multimodal imaging assessed by an independent reading centre masked (blinded) to the treatment arms. This change to the primary endpoint will also align with two ongoing landmark Geographic Atrophy studies underway, the CHROMA (NCT02247479) and SPECTRI (NCT02247531) studies sponsored by Hoffmann-La Roche. Modifying the primary endpoint for CRFB002AAU17 will allow a larger pool of trials and evidence reporting with a common endpoint.

Since the study will recruit patients who are either treatment-naïve in both eyes or, alternatively, treatment naïve in only one eye (i.e. the first/fellow [non-study] eye may be treated with any anti-VEGF), the patients will be stratified at randomisation to ensure an even distribution across the two study groups to account for any potential contralateral effect of the first/fellow eye medication on the study eye. Randomisation will occur within three strata: two treatment naïve eyes, one eye (first/fellow non-study eye) being treated with ranibizumab, and one eye (first/fellow non-study eye) being treated with an anti-VEGF other than ranibizumab.

2 Study objectives

2.1 Primary and key secondary objectives

The primary objective is to investigate the difference between the development of new geographic atrophy in the study eye following intravitreal ranibizumab relative to aflibercept in patients with wet AMD. The primary endpoint for the study will be the mean change in area of geographic atrophy from baseline to month 24 (as measured by OCT and autofluorescence images assessed by an independent masked reading centre).

The key secondary endpoints will be:

- the number of injections from baseline to month 12
- the mean change in BCVA (logMAR) from baseline to month 12

2.2 Additional secondary objectives

Additional secondary endpoints will include:

- the mean change in area of existing and newly developed geographic atrophy from baseline to month 12
- the proportion of patients showing geographic atrophy from baseline to month 12
- the number of injections from baseline to month 24
- the mean change in BCVA (logMAR) from baseline to month 24
- the mean change in central retinal thickness (CRT) from baseline to months 12 and 24
- the proportion of patients showing no intra-retinal and sub-retinal fluid at months 2, 12 and 24
- the proportion of patients showing greater than and equal to 15 letters (logMAR) gain from baseline to months 12 and 24
- the proportion of patients showing less than or more than and equal to 15 letters (logMAR) loss from baseline to months 12 and 24
- the number of times a patient needed to return to monthly treatments during the 24 months
- retinal nerve fibre analysis at baseline and month 24
- the concentration of plasma VEGF at baseline and 7 days post-injection following week 4 and week 8 mandated intravitreal injections in full population and treatment naïve patients ocular and systemic adverse events at all visits
- ocular inflammation at baseline and 7 days post-injection following 3rd mandated intravitreal injection.

3 Investigational plan

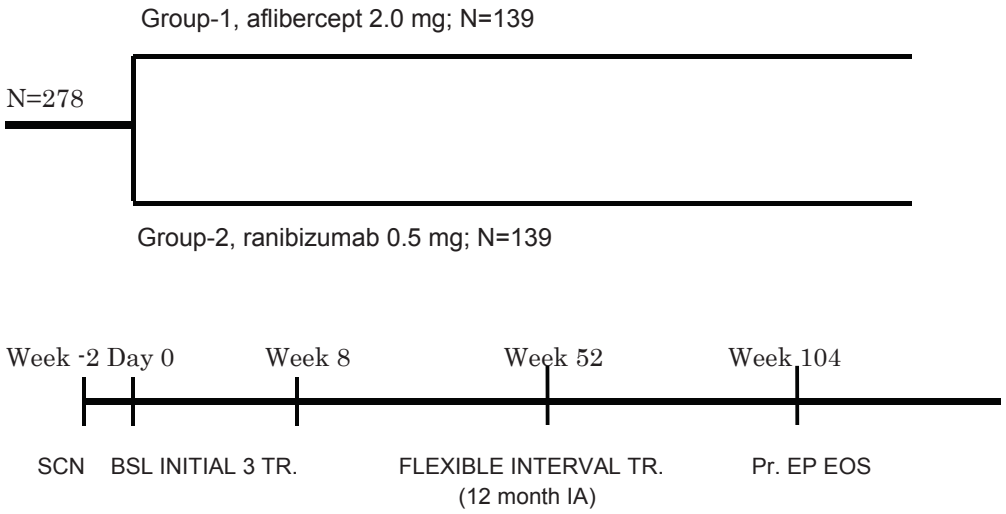
3.1 Study design

This is a randomised, multi-centre trial investigating the risk of developing new geographic atrophy in the study eye of patients treated with aflibercept relative to patients treated with ranibizumab. After consenting to participate in the study, patients will participate in a screening period lasting up to 2 weeks to evaluate patient eligibility. After eligibility confirmation at the Baseline Visit, patients will be randomised in a 1:1 ratio to one of the two treatment arms i.e. 2.0 mg aflibercept or 0.5 mg ranibizumab within the appropriate stratum

depending on the treatment at baseline for the non-study eye i.e. none, ranibizumab or other anti-VEGF therapy. Only one eye will be selected/treated as the study eye. Ranibizumab and aflibercept will be administered monthly for the first 3 injections followed by an individual treatment interval determined by disease activity (described in section 5.5.4.1).

Patients withdrawn from the study prior to completion of the 24 month assessment visit will be asked to return for an Early Discontinuation evaluation 30 days +/- 7 days following their last study visit.

Figure 3-1 Study design



SCN = Screening, BSL = baseline, INITIAL 3 TR. = Initial 3 treatments at 4 weekly intervals both arms, Flexible interval Tr = treatment intervals will differ based on arm and disease activity, Pr. EP = Primary Endpoint, EOS= End of study, IA = 12 Month Data analysis.

3.2 Rationale for Study Design

The current design will test whether aflibercept, via its inhibitory action on VEGF-B (in addition to VEGF-A), exacerbates progression of geographic atrophy in wet AMD patients relative to ranibizumab, which inhibits VEGF-A only. This will be tested by comparing 2.0 mg aflibercept with 0.5 mg ranibizumab using an inject and extend regimen (as defined in section 5.5.4.1) in a parallel group study using a primary endpoint of mean change in area of geographic atrophy from baseline to 24 months.

Stratification of patients at randomisation will ensure an even distribution across the two study groups to account for any potential contralateral effect of the first/fellow eye medication on the study eye. There will be no stratification based on photodynamic therapy with verteporfinin in the fellow eye as only treatment with anti-VEGF therapies may have any potential, should the phenomenon exist, for exerting a contralateral effect on the study eye.

3.3 Rationale for dose, duration and method of administration

The current approved doses of 0.5 mg ranibizumab by intravitreal injection and 2.0 mg aflibercept by intravitreal injection will be used in this study. The current recommended administration for ranibizumab is monthly or, if this is not feasible, quarterly, and for

aflibercept it is monthly for the first 3 months then bi-monthly thereafter (Lucentis Product Information; Eylea Product Information). In practice, ophthalmologists use a more conservative approach based on a prn or inject and extend regimen in which frequency of injections is guided by disease activity (Deloitte Access Economics, 2011). This approach is supported by a number of clinical trials including the PrONTO, CATT and HARBOR ranibizumab studies (Spaide, 2007; Lalwani et al, 2009; Frampton, 2013; Oubraham et al, 2011; Martin et al. 2011; 2012; Busbee et al, 2013) and the 2nd year of the VIEW I and II aflibercept studies (Browning et al, 2012; Stewart, 2012).

This practice will be used for the current study.

Historical data from a number of clinical trials demonstrate that 0.5 mg ranibizumab and 2.0 mg of aflibercept offers the most favourable risk/benefit profile and these are the licensed doses for the treatment of wet AMD in Australia.

Both ranibizumab and aflibercept are administered as intravitreal injections to maximise the bioavailability of the drug at the site of pathology whilst minimising systemic exposure. The 'inject and extend treatment' approach has been demonstrated to yield similar efficacy outcomes to the monthly injection regimen (as referenced above).

The 24 month duration of the study is necessary for a treatment of this type to determine any clinically significant differences or outcomes between the two treatment groups. The CATT study demonstrated that, by 2 years of treatment, there was a statistically significant difference in the number of patients newly developing geographic atrophy based on type of anti-VEGF therapy used (ranibizumab or bevacizumab) and treatment regimen (monthly or prn) (Martin et al, 2012). Further, as yet unpublished clinical observation by the Steering Committee of retinal specialists for this study is that geographic atrophy changes of any clinical significance are not apparent before a minimum of 2 years of anti-VEGF therapy and that a reported mean enlargement rate of geographic area of 2.07 mm^2/ year (Moussa et al, 2013) equating to a change of >4 mm^2 over 2 years has the clinical consequence of negatively impacting visual acuity in patients over the longer term (>3 years and beyond).

A parallel group design for this study is acceptable as the therapies being used are both well established for the treatment of wet AMD. It will allow patient responses to be measured over time as is required to assess the development of geographic atrophy over 24 months.

3.4 Rationale for choice of comparator

Aflibercept is the comparator therapy for this study. The rationale for the choice of aflibercept is that it is currently the only registered and reimbursed alternative medication to ranibizumab that shows comparable visual gains for the treatment of wet AMD in Australia. It is therefore the only appropriate comparator available at present.

3.5 Purpose and timing of analyses / design adaptations

An analysis of the two key secondary endpoints will be conducted after all patients have had 12 months of treatment to explore the treatment algorithm for anti-VEGF therapy described specifically in this study. The question of the inject and extend regimen and subsequent injection frequency between ranibizumab and aflibercept is of great clinical interest in the ophthalmology community (medical retina subspecialty) since a randomised, controlled trial has not been previously performed to investigate outcomes using an inject and extend regimen for either drug (published treatment regimens for ranibizumab are limited to monthly and prn, and for aflibercept 3 monthly followed by 8 weekly in year 1 followed by prn in year 2). The analysis will explore specifically the number of injections and mean change in BCVA from baseline to month 12. While no power analysis was undertaken directly for these early

measurements, the sample size estimated for the primary endpoint was assessed as to its adequacy for addressing the question of number of injections at 12 months. As the study is masked at the level of the central reading centre only, it will be possible to analyse these two endpoints when 12 month data are available without compromising the ongoing conduct of the study. This is the only analysis that will occur before the end of the study. The primary endpoint and all other secondary endpoints will only occur at the conclusion of the study.

3.6 Risks and Benefits

The main risks of the study relate to the actual intravitreous injection itself. In the first instance, injections of drug into the vitreous cavity have inherent risks, both ocular (such as endophthalmitis, lens trauma and retinal detachment) and systemic (arterial thromboembolic events) so that limiting the number of injections would be desirable if the same visual acuity result could be achieved. The ocular and systemic risk profile for ranibizumab has been clearly described for monthly injections (up to 24 months) in the pivotal ANCHOR and MARINA studies (Lucentis Product Information), and for less than monthly injections in the CATT and HARBOR studies (Martin et al, 2012; Busbee et al, 2013) so no new risks are anticipated as a result of this present study. The ocular and systemic risk profile for aflibercept has been clearly described for monthly injections and for three consecutive monthly injections followed by bi-monthly (both treatment arms for 12 months) followed by capped (at 12 weeks) prn (Heier et al, 2012; Eylea Product Information) so no new risks are anticipated as a result of this present study.

The risk to subjects in this trial will be minimised by compliance with the inclusion/exclusion criteria and close clinical monitoring for any adverse effects as a result of the treatment.

4 Population

This will be a multi-centre study conducted in approximately 21 sites across Australia and New Zealand, recruiting patients diagnosed with visual impairment due to wet AMD. Each site will recruit approximately 15 patients. A total of 278 will be recruited to this study, with 139 patients randomised to each arm. This accounts for a drop-out rate of 15% over 2 years. Assuming an approximate 20% screen failure rate, approximately 333 patients will need to be screened to have 278 patients found eligible and commencing treatment in the trial.

4.1 Inclusion criteria

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

Inclusion criteria for patient:

1. Written informed consent must be obtained before any study-related assessment is performed.
2. Male or female patients ≥50 years of age.

Inclusion criteria for study eye:

3. Diagnosis of active subfoveal CNV secondary to wet AMD without restriction of lesion size, with visual impairment being exclusively due to an active wet AMD lesion. Active lesions will be characterised by any of the following: abnormal retinal thickness, with evidence of intraretinal, subretinal or sub-pigment epithelial fluid accumulation, confirmed by OCT; presence of intraretinal or subretinal haemorrhage; leakage shown

on a FA unless solely due to dry, fibrotic staining; visual acuity deterioration considered likely to represent CNV.

4. BCVA score at both Screening and Baseline must be 23 letters or more as measured by the 3 metre Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts, inclusively (or approximate Snellen equivalent to 3/60+3).

If both eyes are eligible at Screening and Baseline, the investigator will decide the study eye based on clinical judgment. Only one eye needs to meet the study entry criteria.

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study.

Exclusion criteria for patient:

1. Inability to comply with study or follow-up procedures.
2. Pregnant or nursing (lactating) women.
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 sterilisation (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 sterilisation (at least 6 m prior to screening). For female subjects on the study, the vasectomised 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. 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.

5. Stroke or myocardial infarction less than 3 months prior to Screening.
6. Uncontrolled blood pressure defined as systolic value of >160 mm Hg or diastolic value of >100 mm Hg at Screening or Baseline.
7. Known hypersensitivity to ranibizumab or aflibercept or any component of the ranibizumab or aflibercept formulation, or fluorescein.

Exclusion criteria for ocular medical history and conditions:

For both eyes:

8. Any active periocular or ocular infection or inflammation (e.g., blepharitis, conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) at the time of Screening or Baseline.
9. 1 or more patches of geographic atrophy $\geq$ 250µm in longest linear dimension.
10. Uncontrolled glaucoma (intraocular pressure [IOP] ≥30 mm Hg on medication or according to investigator's judgment) at the time of Screening or Baseline.
11. Neovascularisation of the iris or neovascular glaucoma at the time of Screening or Baseline.
12. Inability to obtain multimodal images of sufficient quality to be analysed.

For study eye:

13. Visually significant cataract (likely to require surgery within the next 12 months), aphakia, severe vitreous haemorrhage, rhegmatogenous retinal detachment, proliferative diabetic retinopathy or CNV of any cause other than wet AMD (e.g., ocular histoplasmosis, pathologic myopia macular hole) at the time of Screening and Baseline.
14. Structural damage within 0.5 disc diameter of the centre of the macula (e.g., vitreomacular traction, epiretinal membrane, scar, laser burn, foveal atrophy) at the time of screening that in the investigator's opinion could preclude visual function improvement with treatment.

Exclusion criteria for prior or current systemic medication:

15. Use of other investigational drugs within 30 days or 5 half-lives from baseline, whichever is longer.
16. Current or planned use of systemic medications known to be toxic to the lens, retina or optic nerve as outlined in the Lucentis and Eylea Product Information.

Exclusion criteria for prior or current ocular treatment:

For study eye:

17. Treatment with any anti-angiogenic drugs (including any anti-VEGF agents) prior to Baseline in eye.
18. Any intraocular procedure (including Yttrium-Aluminium-Garnet capsulotomy) within 2 months prior to Baseline or anticipated within the next 6 months following Baseline.

Exclusion criteria of prohibited treatments (study eye):

19. Intra or periocular corticosteroids (including sub tenon but excluding topical formulations)
20. Intraocular corticosteroid implants

PLEASE NOTE REGARDING TREATMENT FOR FELLOW EYE:

Treatment with any anti-angiogenic drug (including any anti-VEGF agents) is allowed prior to Baseline in fellow eye.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

The investigational treatment/study drugs in this study are 2.0 mg aflibercept and 0.5 mg ranibizumab.

Aflibercept is available for use in Australia and New Zealand for the treatment of wet AMD. In Australia, it is reimbursed and thus available on the Pharmaceutical Benefits Scheme (PBS); it is not reimbursed in New Zealand and thus will be supplied for patients by the study sponsor. Aflibercept is supplied as a solution for injection in a single use glass vial providing 0.05 ml of 40 mg/mL for intravitreal injection.

Ranibizumab is available for use in Australia and New Zealand for the treatment of wet AMD. In Australia, it is reimbursed and thus available on the PBS; it is not reimbursed in New Zealand and thus will be supplied for patients by the study sponsor. Ranibizumab solution for injection is commercially supplied in vials with each vial containing ranibizumab in the concentration of 10 mg/ml (0.5 mg/0.05 ml, corresponding to a 0.5 mg dose level) and as 0.165 mL sterile solution in a pre-filled syringe. Vials and pre-filled syringes of ranibizumab are for single use only.

5.1.2 Additional study treatment

No additional treatment beyond the investigational and reference treatments is requested for this trial.

5.2 Treatment Arms

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

Arm 1. 2.0 mg aflibercept – administered monthly for the first three injections, followed by an individualised treatment interval determined by disease activity as described in section 5.5.4.1.

Arm 2. 0.5 mg ranibizumab – administered monthly for the first three injections, followed by an individualised treatment interval determined by disease activity as described in section 5.5.4.1.

Please see Section 5.5.4.1 for detailed description of the inject and extend treatment regimen.

5.3 Treatment Assignment, Randomisation

At Visit 2, all eligible patients will be randomised via Interactive Web-based Response System (IWRS) to one of the treatment arms. The investigator or his/her delegate will confirm that the patient fulfils all the inclusion/exclusion criteria and identify to which stratum they belong. The IWRS will link the patient to a treatment arm.

At subsequent visits after randomisation, the decision to administer treatment to the patient will be made according to the treatment regimen (as described in Section 5.5.4.1) and in line with the treatment group assignment at randomisation.

5.4 Treatment blinding/Masking

Due to logistical difficulties of masking at the investigator site (requiring two independent ophthalmologists to act as assessor and injector) and to avoid introduction of investigator bias in retreatment decisions, a central reading centre will be employed to mask the study for the primary endpoint and for secondary endpoints which rely on imaging of the eye. The central reading centre will be masked to the randomisation and treatment of the patient. All images collected during the study (OCT, FA, AF & Colour Fundus), will be sent to the masked central reading centre. During the inject and extend phase of the protocol (Week 8 onwards), the investigator will review the patient results so as to determine the appropriate treatment interval per section 5.5.4.1. However, prior to the next scheduled visit for the patient, the central reading centre will communicate to the investigator a recommendation of when this next visit should occur based on analysis of the images. The investigator should adjust the visit schedule in line with the central reading centre recommendation. Information sent to the central reading centre will be de-identified and will include confirmation of disease activity criteria per section 5.5.4.1 to allow this assessment. The sponsor of the trial, through the monitoring process, will be able to review protocol compliance based on the recommendations provided by the masked central reading centre and the visit schedule as captured in the eCRF during the study.

So as to ensure that the measurement of BCVA scores is not influenced by bias, it is the investigator' responsibility to ensure that a qualified person is appointed for assessment of BCVA scores and that this person is masked to the treatment assignment. The initials of the BCVA assessor will be captured to enable an in study review of compliance in this respect. On site monitoring by Novartis will confirm that adequate measures have been taken to maintain the masking of the BCVA assessor.

The patient should be kept masked to their treatment allocation by the investigator.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her centre number and patient number. The centre number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 00001, and subsequent patients are assigned consecutive numbers (e.g. the second patient is assigned patient number 00002, the third patient is assigned patient number 00003).

Once assigned to a patient, the patient number will not be reused. If the patient fails to be randomised for any reason, the IWRS should be notified that the patient was not randomised.

The reason for not being randomised will be entered on the electronic case report form (eCRF).

5.5.2 Dispensing the investigational treatment

In Australia, ranibizumab and aflibercept are commercially available through prescription by the treating ophthalmologist. Medication will be prescribed and dispensed following standard, Australian clinical practice complying to regulatory and reimbursement requirements. Since ranibizumab and aflibercept are not reimbursed in New Zealand, the drug will be provided by the Sponsor specifically for New Zealand patients.

5.5.3 Handling of Treatment Medication

Both ranibizumab and aflibercept should be kept in a secure location and the vials should be kept in the outer carton to protect from light until needed. Ranibizumab and aflibercept should be stored at 2°C to 8°C (refrigerate - do not freeze) as per the approved product information (Lucentis Product Information, Eylea Product Information).

5.5.4 Instructions for prescribing and taking treatment

For the entire trial, regardless of randomisation, the following rule applies: ranibizumab or aflibercept should be administered in the study eye on the day of the study visit or, if this is not possible, within 7 days after the occurrence of the study visit. In any case, study treatment has to occur within the visit window as indicated in table 6.1.

Instructions on how to prepare and administer ranibizumab or aflibercept for intravitreal injection should follow the approved Prescribing Information for each medication.

5.5.4.1 Treatment Regimens

Screening Period: Week -2 to Baseline Visit

At Screening (Visit 1 to occur up to 2 weeks before Baseline [Visit 2]), after signing the informed consent, patients are enrolled into the study and procedures are performed to allow assessment of the study eligibility criteria. Patients will be assessed for study eligibility by assessment of visual acuity using logMAR, stereoscopic biomicroscopic slit-lamp fundus examination (78 D or similar lens), FA and OCT.

Once eligibility is confirmed they will be randomised to one of two arms:

Arm 1: 2.0 mg aflibercept OR **Arm 2: 0.5 mg ranibizumab**

Initial Treatment Period: Baseline to Week 8 (Visit 2,3,4)

Regardless of the treatment arm to which the patient is randomised, all patients will have three monthly injections of either 2.0 mg aflibercept or 0.5 mg ranibizumab in the elected study eye, according to the treatment arm to which the patient is assigned, at Baseline, Week 4 and Week 8.

Treatment Period: Week 8 (Visit 4) to Week 104 (Month 24)

The patient will receive either 2.0 mg aflibercept or 0.5 mg ranibizumab in the elected study eye, according to the treatment arm to which they are assigned, at each treatment visit.

At Week 8 (Visit 4), the patient will be treated and the interval before the next treatment visit will be determined by their disease activity as defined below.

At Week 8 (Visit 4), the patient will receive their third injection of study treatment and the central reading centre will assess for disease activity in the study eye as defined by:

- a loss of VA of ≥5 letters than the best VA recorded since treatment started (Where VA loss is considered, by the investigator, to be due to disease activity);
- new retinal haemorrhage;
- the presence of any IRF or SRF on OCT.

If any of these signs of disease activity are present in the study eye, either singularly or in combination, the subsequent injection visit interval is kept at 4 weeks (i.e. 28 day interval; no increase in the treatment interval). If none of these signs of disease activity are present, the subsequent injection interval is extended to 6 weeks. This process occurs with a 2 week extension until 12 weekly intervals are reached; there is no increase past 12 weekly.
If there are any signs of disease activity in the study eye at any given interval, then the subsequent injection interval is not increased.

Once treatment interval extension has occurred, the presence of disease activity in the study eye will require a reduction in the treatment interval as follows:

- If one (1) sign of disease activity, as defined above, is seen then the interval is reduced by 2 weeks.
- If two (2), or more, signs of disease activity, as defined above, are seen then the interval of injections is reverted back to 4 weekly injections.

The interval is further decreased (if not at 4 weeks) at the subsequent visit(s) if signs of activity are detected using this approach.

The minimum injection interval for both medications is 4 weeks.

Extension will again occur at a subsequent visit if there are no signs of disease activity. However, on the fourth extension, or any extension thereafter, the maximum interval will be 2 weeks less than the maximum interval at which disease activity previously occurred in any of the three previous extensions (referred to as the break point). The patient will continue at the break point treatment interval for the rest of the study unless they have signs of disease activity listed above.

Follow-up Period: Month 24

Where a patient has had their last study injection prior to the Month 24 visit window the patient will return for final efficacy and safety assessments at Month 24. Week 103 is the last possible visit in the study at which a patient may receive an injection. If a patient requires an injection at week 104 (Month 24), the visit assessments will be performed as part of the study then the injection may be administered subsequently but not as part of the study.

5.5.4.2 Treatment of the fellow eye

Patients that develop visual impairment due to wet AMD in the fellow eye (non-study eye) during the study that, in the investigator's opinion, qualifies for and requires treatment may be treated with any medication in accordance with the country's standard of care. This eye is

then called the fellow treated eye.

Treatment of the fellow eye must be scheduled in a way so as not to disturb the schedule for visits and treatments of the study eye. It must be recorded in the eCRF each time treatment has been administered to the fellow eye.

5.5.4.3 Permitted dose adjustments and interruptions of study treatment

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

Adjustments of the dosing regimen of ranibizumab or aflibercept outside of that described as part of the study treatment administration in Section 5.5.4.1 are not permitted.

Ranibizumab or aflibercept 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.

If study medication is withheld, the reason for the interruption of treatment and date of interruption should be appropriately documented in the source documents as well as in the eCRF.

5.5.5 Rescue Medication

No rescue medication is permitted in this study.

5.5.6 Concomitant Medication

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

5.5.7 Prohibited Treatment

Use of treatments, as displayed in Table 5-1are NOT allowed after the start of study i.e., screening. Use of these treatments after the start of the study require that the patient be withdrawn from the study (See 5.5.8).

Table 5-1 Prohibited treatment

Medication	Action to be taken
Anti-VEGF drugs other than ranibizumab & aflibercept (ocular or systemic) - study eye	Study withdrawal
Intra- or periocular corticosteroids (including sub Tenon but excluding topical formulations) – study eye	Study withdrawal
Intraocular corticosteroid implants – study eye	Study withdrawal
Investigational drugs and interventions - any type	Study withdrawal

5.5.8 Discontinuation of study treatment and premature patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. Patients may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on the relevant study completion page in the eCRF. Study treatment must be discontinued.

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

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.

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 5.5.7), unacceptable AEs, refusal to continue treatment, or at the investigator's discretion based on 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 any of the following AEs:
    - Full thickness macular hole (Gass stages 2,3 or 4)
    - Stroke or transient ischemic attack
    - Rhegmatogenous retinal detachment
    - Pregnancy
    - Unsatisfactory therapeutic effect
- Any other protocol deviation that results in a significant risk to the patient's safety

- Use of prohibited treatment in Table 5-1
- Patient's condition no longer requires study treatment
- Administrative problems (e.g. patient's non-compliance)

Patients who permanently discontinue study treatment and start a prohibited non-study treatment (see Section 5.5.7) should be withdrawn from the study and undergo all assessments for Month 24/Early Discontinuation Visit as described in Table 6-1.

In addition to scheduled visits, patients who discontinue study drug due to adverse events or abnormalities on safety monitoring tests must be followed up with additional visits as needed in order to confirm the resolution of abnormalities.

A treatment period completion form in the eCRF should be completed, providing the primary reason for stopping study treatment.

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

5.5.9 Emergency breaking/ Unmasking of treatment assignment

Not applicable to this study as investigators are not masked to treatment assignment.

5.5.10 Study completion and post-study treatment

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 Month 24 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.

No extension study has been planned.

5.5.11 Early Study Termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and undergo assessments as described in Table 6-1 for an Early Discontinuation Visit. 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 IRB/EC of the early termination of the trial.

6 Visit Schedule and Assessments

Table 6-1 lists all of the assessments and procedures to be performed at each study visit.

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 0) for all patients. Study assessments will be performed at Screening (Visit 1), Baseline (Day 0, Visit 2) and at Visits 3 and 4 as per the study schedule. After Visit 4 and then through to Month 24 (Week 104), the visit intervals will be determined by the patient's disease activity as per section 5.5.4.1. Visit windows are applied as indicated in table 6-1 to allow for flexibility in scheduling for all visits.

However, it is essential that the treatment period be strictly adhered to during the period of the first three consecutive doses. Further, it is essential that the shortest interval between ranibizumab doses be ≥28 days.

An unscheduled visit may occur at any time throughout the study due to an AE or any other reasons. All information obtained from any assessments performed during an unscheduled visit must be also supported in the patient's source documentation and recorded in the eCRF.

Table 6-1 Assessment schedule

Period	Screen	Initial Treatment					Treatment Period			
Visit	**1**	**2**	**3**	**Visit 3+ 7days**	**4**	**Visit 4+ 7days**	**n**	**Month 12†**	**n**	**Month 24 or Early Discontin -uation**
Weeks (relative to Baseline, Day 0)	**-2 to 0**	**Baseline**	**4**	**5**	**8**	**9**	**v**	**52**	**v**	**104**
Visit window (days)			**±3**	**±3**	**±3**	**±3**	**±7**	**± 6**	**± 7**	**±6**
Informed Consent	X									
Assign Patient Number	X									
Review of inclusion/exclusion	X	X								
Review of withdrawal criteria		X	X		X		X	X	X	
Demography	X									
Medical history	X									
Prior/concomitant medication	X	X	X		X		X	X	X	X
Pregnancy test	Xs									Xs or u
Randomisation		X								
Plasma VEGF	X			X		X				
Vital signs	X	X						X		X
BCVA score(logMAR)	Xf & r^	Xf & r**	X		X& r		X	Xf & r	X	Xf & r
Ophthalmic examination	Xf	Xf	X		X		X	Xf	X	Xf
Optical coherence tomography	Xf	Xfe	Xe		Xe		Xe	Xfe	X	Xfe
Autofluorescence	Xf	Xf	Xf		Xf			Xf		Xf
Colour fundus photography	Xf**	Xf**	X*		X*		X*	Xf	X*	Xf
Fluorescein angiography	Xf**	Xf**			Xf			Xf		Xf
Nerve Fibre Analysis		X						X		X
Intraocular Inflammation		X				X				
Study Treatment		X	X		X		X	X†	X	
Adverse events	X	X	X	X	X	X	X	X	X	X
IWRS entry	X	X								X

Key: n = number of visits as required per protocol section 5.5.4.1
v = variable. The number of visits will differ dependent on treatment interval as per protocol section 5.5.4.1
Xf = Procedures to be which performed for both eyes (study and fellow eye)
e = Enhanced Depth Imaging (EDI). To be collected by sites with the Heidelberg OCT machine.
^ = To determine eligibility BCVA score at Screening must be 23 letters or more as measured by the 3 metre Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts, inclusively **or** approximate Snellen equivalent to 3/60+3
s = serum
u = urine
* =Optional if haemorrhage is present in study eye and Colour Fundus is required
** = Fluorescein angiography and colour fundus photography images that were performed under normal clinical practice will be accepted if performed no more than 14 days prior to the baseline visit. For all other visits the protocol as described in the manual provided by the central reader, should be followed.
If there is no more than 48 hours between the screening and baseline visit, and the screening BCVA was measured by the 3 metre Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts there is no requirement to repeat BCVA for the baseline visit.
r = Visual Assessments requiring refraction

†= If patient is not due for another injection within the visit window of the Month 12 the patient should attend a visit and have all procedures except ranibizumab or aflibercept injection.

6.1 Information to be collected on screening failures

Patients will undergo screening procedures after providing written informed consent (See 10.2).

Patients who are screened but determined not eligible for treatment are considered screening failures. The reason for screening failures will be documented on the Screening Log. In addition, the demography information and serious adverse event (SAE) data will be collected for all screening failures in the eCRF.

For screen failure patients, adverse events that are not SAEs will be followed by the investigator and collected only in the source data. SAEs will be reported immediately as per 7.2.

For all patients who have signed informed consent and are randomised into the next period of the study, all AEs **occurring after informed consent is signed** will be recorded on the relevant AE eCRF.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever in their judgment, the test abnormality occurred before the informed consent signature.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristics to be collected for randomised patients include:

- Demography: date of birth, gender, race, ethnicity
- Relevant medical history/current medical condition data includes data until the informed consent is signed. Where possible, diagnoses and not symptoms will be recorded
- Study eye selection
- Baseline characteristics

Other assessments performed at Screening to determine eligibility are listed in Table 6-1.

6.3 Treatment Exposure and Compliance

Treatment exposure to ranibizumab or aflibercept will be assessed for both study eye and fellow treated eye. Information regarding study treatment administration (ranibizumab or aflibercept) in the study eye will be collected on the drug administration record of the eCRF.

Treatment of the fellow eye will be captured on a separate eCRF page.

In instances of missed doses, the reason will be described on the drug administration record of the eCRF for the corresponding eye or eyes.

Compliance to treatment regimen

The evaluation of the investigator's assessments will be compared to treatment decision – i.e. if injections were administered to the study eye in line with the regimen of the assigned treatment group. An independent review of fundus photography, FA, OCT and autofluorescence images for patients enrolled in the study will be performed at a masked central reading centre. During the inject and extend phase of the study, the decision regarding the interval of time to the next injection will be made by the investigator as per 5.5.4.1. However, the central reading centre, which will be masked to the treatment, will confirm the investigator's decision or mandate an alternative interval based on the

assessment of the fundus photography, OCT and autofluorescence images and specified retreatment criteria for both arms of the study.

6.4 Efficacy

All efficacy assessments are to be done on the study eye and recorded in the relevant eCRF.

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

The CRC will provide sites with a Study Manual and training materials for the specified study ocular images. All images will be obtained by trained site personnel at the study sites and forwarded to the CRC for independent standardized analysis and storage.

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

Study eye selection:

If both eyes are eligible for the study the investigator will designate the study eye at his/her discretion at the screening visit and will confirm his/her decision at the baseline visit. This decision and confirmation needs to be documented in the relevant eCRF and in the source documents of the patient. The study eye should be naïve to previous therapy and is the one treated with the study treatment and assessed according to protocol requirements as outlined in the assessment schedule (Table 6-1). Data collected on the study eye are used for the evaluation of efficacy objectives of the study. At visits when ranibizumab or aflibercept treatment is administered, an ocular examination and efficacy assessments must be conducted prior to administration of that treatment.

6.4.1 Colour fundus photography and fluorescein angiography (FA)

Macular colour fundus photography will be performed in both the study and fellow eye at Screening/Baseline, Month 12 and 24. If a new haemorrhage is found in the study eye, then colour fundus photograph should be taken at the relevant visit to confirm presence. FA will be performed in both the study and fellow eye at Screening/Baseline, Week 8, Month 12 and 24. The images will be evaluated by a central reading centre to determine the presence and the type of AMD and area of leakage. There will be no requirement for central reading centre confirmation of patient eligibility to study sites before patient enrolment in the study.

Photography and FA performed within 14 days before the Baseline Visit will be accepted as the baseline examination (will not need to be repeated unless clinically indicated).

6.4.2 Visual Acuity

Visual acuity will be performed by an assessor (masked to the randomisation and treatment of the patient) using a logMAR chart at all visits. BCVA with refraction will be performed in the study eye at Screening/Baseline, Week 8, and Months 12 and 24, and in the fellow eye at Screening/Baseline and Months 12 and 24. If it is not possible to perform a subjective refraction or visual acuity testing due to any reason, including visual acuity is too poor for the patient to read at least 3 letters on the refraction/visual acuity chart, the refraction/visual acuity testing should be attempted at 1 metre. 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 by an accredited vendor chosen by the sponsor 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 relevant eCRF.

6.4.3 Autofluorescence

Autofluorescence will be performed for the study and fellow eye to measure the presence of existing geographic atrophy at Screening/Baseline, Week 4 & 8 and the expansion of existing geographic atrophy and newly developed geographic atrophy at Month 12 and 24. A masked central reading centre will evaluate geographic atrophy for the primary endpoint. As the initial image may be obstructed by haemorrhage, the CRC may use the clearest of the initial 3 readings as the baseline value.

6.4.4 Optical Coherence Tomography (OCT)

OCT images are to be taken using High Definition (HD)/Spectral Domain (SD) (OCT) equipment to assess central retinal thickness and the presence of IRF and/or SRF. Patients must be assessed using the same machine throughout the course of the study.

The investigator will perform OCT at all visits as indicated in Table 6-1. The information collected will be used by the investigator to assess the status of disease activity i.e., decisions with regard to treatment extension are based on investigator evaluation and confirmed by the central reading centre in accordance with the retreatment criteria outlined in sections 5.5.4.1 and the reading centre procedures as outlined in section 5.4.

There will be centralised reading of all OCT images collected throughout the study. Details of this will be recorded in an OCT manual provided by the central reading centre.

Enhanced Depth Imaging (EDI) images should be taken by sites using the Heidelberg OCT machines as per the CRC manual.

6.4.5 Appropriateness of Efficacy Assessments

Evaluations described in this protocol are standard ophthalmic assessments in this indication and are required to enable 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. Methods applied for the evaluation of safety include ophthalmic examinations and vital signs. These assessments are performed according to the schedule in Table 6-1.

Significant findings that are present prior to signature of the informed consent must be included in the Relevant Medical History/Current Medical Conditions eCRF. Significant findings made after the signature of the informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event eCRF.

All ocular assessments enabling identification of possible adverse events will be performed on both the study and fellow eye.

6.5.1 Ophthalmologic Exams

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 or

aflibercept. In the study eye, tonometry should be conducted at every study visit in both treatment groups to assess IOP, regardless of treatment administration afterwards, based on investigator discretion. On visits when ranibizumab or aflibercept treatment is administered, also post-injection tonometry may be performed as per investigator discretion between 15 and 60 minutes after treatment in the study eye. It is recommended that reference is made to the TGA approved Lucentis Product Information and Eylea Product Information.

If study visit assessments and a corresponding treatment occur on separate days, a repeat ophthalmoscopy should be performed as a safety check before treatment of the study eye.

6.5.2 Fellow eye

In order to characterise the patient and collect safety data, ophthalmic examination, FA, BCVA, OCT, colour fundus photography and autofluorescence will be performed in the fellow-eye (treated or not treated) at Baseline, Month 12 and Month 24/Early Discontinuation Visit. Data will be documented in the source documents and also recorded in the eCRF as applicable.

If the fellow eye presents with wet AMD it may be treated according to the country's standard of care, at the discretion of the investigator. The fellow eye treated is then labelled the fellow treated eye. At the time when treatment of the fellow eye is being initiated, the BCVA assessment should be repeated.

6.5.3 Physical Exam

No physical examination will be performed except for Vital Signs.

6.5.4 Vital Signs

This includes assessment of the sitting blood pressure (systolic, diastolic) at screening, baseline and Month 24/Early discontinuation visit. The results will be recorded in the relevant eCRF.

6.5.5 Laboratory Investigations

No laboratory evaluations to assess blood or urine parameters will be performed – with the exception of pregnancy assessments as described in Section 6.5.7. Plasma VEGF assessments will be performed as described in Section 6.6.1.

6.5.6 Electrocardiogram (ECG)

No ECG will be performed

6.5.7 Pregnancy

During the study period, all women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use an effective method of contraception. 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 sterilisation (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 sterilisation (at least 6 months prior to screening). For female subjects on the study, the vasectomised 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.

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test at the screening visit and results will be recorded in the source documents and on the eCRF. Where possible, a local laboratory will be used for analysis of the serum. Where not possible, the sponsor may enlist a central laboratory. A positive result will exclude the patient from participation in the study. If a patient becomes pregnant between Screening and Month 24, they will be discontinued from study treatment and followed until completion of the pregnancy and the outcome will be reported. A urine or serum pregnancy test, as is most convenient for the site, will be done at Month 24. Any instances of pregnancy will be reported as per section 7.3.

6.5.8 Appropriateness of Safety Measurements

The safety assessments selected for this study are standard for this indication and patient population. In addition, intraocular inflammation will be measured at baseline and 7 days post-injection following the 3rd mandated intravitreal injection to determine if there is a difference in the risk of inflammation with either aflibercept or ranibizumab.

6.6 Other Assessments

6.6.1 Plasma VEGF

Blood for plasma VEGF is being collected at Screening and again at 7 days (+/- 3 days) after the injection at Week 4 (Visit 3) and 7 days (+/- 3 days) after the injection at Week 8 (Visit 4).

The purpose of the plasma VEGF measurements is to determine if aflibercept and ranibizumab inhibit systemic VEGF levels to a differing degree by virtue of their distinct difference in systemic half-life post-intravitreal injection. This has consequences potentially on the rates of systemic adverse events, particularly arterial thromboembolic events, which have been described for both aflibercept and ranibizumab. A venous blood sample will be collected from each patient using a central lab facility and stored for subsequent measurement of plasma VEGF.

7 Safety monitoring

7.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavourable 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. All adverse events must be recorded on the Adverse Events eCRF with the following information:

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

An SAE is 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 hospitalisation or prolongation of existing hospitalisation, unless hospitalisation is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since 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 jeopardises the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

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

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalised/patient's hospitalisation prolonged. The action taken to treat the adverse event should be recorded on

the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent. 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 for ranibizumab already known about the investigational drug can be found in the Product Information leaflet or will be communicated in the form of Investigator Notifications. Information about common side effects for aflibercept already known about the investigational drug can be found in the product information leaflet. 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 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 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 Investigator's Brochure or 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 local regulatory requirements.

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 outcomes must be collected for the female partners of any males who took investigational product in this study. Consent to collect information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy should be recorded on a Clinical Trial 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 pregnancy must be reported on the SAE Report 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 the eCRF with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the relevant recording method chosen, the adherence to the protocol and to Good Clinical Practice, the progress of enrolment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on the relevant 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 relevant eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the relevant 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 Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the eCRF system until they have been trained. Automatic 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 Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

8.3 Database Management and Quality Control

Novartis staff, or 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.

Data queries are created, issued to the sites, and tracked through the eCRF system. They are either generated automatically, via programmatic edit checks, or manually generated by the Monitor during source document verification (SDV) or Data Management during data review and reconciliation activities.

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

FA, OCT and autofluorescence readings will be processed centrally and the results will be sent electronically to Novartis and the CRO working on behalf of Novartis.

8.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be required for this study. The recent VIEW 96 weeks (Schmidt-Erfurth 2014) publication found no significant differences in safety or efficacy when both were used on a PRN regimen at 2 years.

8.5 Adjudication Committee

Central reading of OCT, autofluorescence and other assessments will occur in a masked fashion. This blinded assessment will be used for data analysis of primary and secondary endpoints as well as to assess compliance with the treatment intervals requirement in each treatment group.

9 Data analysis

All analyses will be performed by a designated CRO.

One analysis is planned when all patients randomised in the study have completed the Month 12 visit (see 9.6, 12 Month Data Analysis).

All other endpoint analyses are planned when all patients randomised in the study have completed the Month 24 visit (or a final visit before or at Month 24) and the Month 24 database has been locked.

Based on this Month 24 database lock, the primary endpoint analysis and remaining

secondary endpoints analyses (i.e. including safety) will be conducted.

Descriptive statistics (n, mean, standard deviation, median, minimum and maximum values and, where appropriate, confidence intervals for continuous variables; frequencies and percentages for categorical variables) 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 but who do not enter the treatment period data will only be listed.

Further technical details and discussions of the following statistical considerations will be provided in the Statistical Analysis Plan (SAP).

9.1 Analysis sets

The **Randomised Population** will consist of all randomised patients.

The **Full Analysis Set (FAS)** compromises all subjects randomised and who have at least one post-baseline efficacy value for the primary endpoint. Following the intent-to-treat principle, subjects will be analysed according to the treatment regimen they were assigned to at randomisation.

The **Per Protocol Set (PPS)** will consist of all patients in the FAS who followed the treatment regimen as randomised and completed the study without clinically significant protocol deviations.

Clinically significant protocol deviations will be identified and documented prior to the database lock.

The **Safety Set** will consist of all patients who received at least one application of study treatment and had at least one post-baseline safety assessment. The statement that a patient had no adverse events also constitutes a safety assessment. Subjects will be analysed according to the treatment regimen they received.

All efficacy evaluations will be carried out on the FAS. The analysis for the primary efficacy evaluation will be carried out on both the FAS and the PPS population. All safety evaluations will be carried out on the Safety population.

Additional analysis sets maybe added and will be detailed in the SAP.

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 summarised as appropriate with descriptive statistics.

Analyses will be based on Randomised Population.

9.3 Treatments

Study Treatment

Descriptive statistics will be provided for exposure to study treatment using the Safety Set. The number of ranibizumab and aflibercept injections will be presented by treatment group in frequency tables by visit and cumulatively. Summaries will be presented for the injections in the study eye and the fellow treated eye as appropriate.

Analyses of the treatment exposure and treatment patterns of the two alternative treatments over 24 months include: treatment frequency (total number of injections), reason for treatment (as defined within disease activity for each arm), the interval between treatments (the first, second and third intervals) and the number of times the patient returns to monthly treatments. Details of the analysis methods will be provided in the SAP.

Concomitant therapies

The number and percentage of patients taking concomitant therapies will be summarised 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 and key secondary variable(s)

The primary objective is to evaluate the difference in the mean change in area of geographic atrophy in the study eye between two treatments from baseline to 24 months.

Key secondary endpoints include assessment of the mean change in BCVA from Baseline to Month 12 and the number of injections from Baseline to Month 12 that will be assessed. A mixed model (see below) utilising all data will be the primary analysis to assess these endpoints in the one analysis with no imputation for missing data. Sensitivity analyses will be conducted as described below..

All significance tests will be 2-sided and differences will be declared statistically significant if $p<0.05$.

The assessment of injection frequency and BCVA when 12 month data are available for all subjects will have no impact on the powering of the primary endpoint.

9.4.1 Key variable(s)

The primary efficacy variable is:

- the mean change in area of geographic atrophy from Baseline to 24 months.

The key secondary variables are:

- the number of injections from Baseline to Month 12
- the mean change in BCVA from Baseline to Month 12.

All data will be summarised by timepoint and treatment group using descriptive statistics. Full details of allocation of assessments to timepoints will be provided in the SAP. All data will be listed.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will be conducted using the FAS.

A mixed model will be fitted with treatment as a factor. Using a modelling approach allows other variables of interest to be included in the model if required, for example age or time since diagnosis of AMD. Details of additional covariates, if any, will be defined in the SAP.

The null hypothesis is that there is no difference between the treatments in the development of new geographic atrophy from Baseline to 24 months. The two treatments will be declared different if the p-value for the treatment effect is <0.05. Ranibizumab will be assessed against aflibercept and found superior if the mean area of geographic atrophy is less than that for aflibercept.

Handling of missing values/censoring/discontinuations

For the primary analysis there will be no imputation for missing data. For secondary and sensitivity analysis, the area of geographic atrophy at the last on-study visit will be used for patients who withdraw prior to the 12 or 24 month visit. A sensitivity analysis will be undertaken using time-to-event techniques where the time to geographic atrophy for patients who withdraw or complete the study prior to developing geographic atrophy will be censored at the time they left the study.

There will be no imputation for missing data for analyses of secondary efficacy variables. Most analyses will consist of using the mixed model approach where all values recorded for each patient up to the time of withdrawal (or completion) are used. This is an appropriate model for data missing at random. Sensitivity analyses may be conducted to explore the robustness of the data to the methods of dealing with missing data. These methods may include LOCF and multiple imputations. The full details of these analyses will be documented in the SAP.

9.4.3 Supportive analyses

. Sensitivity analyses will be described in the SAP. In addition the primary model will be fitted to the per protocol population as a supporting analysis.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Secondary efficacy variables include the number of injections from Baseline to Month 12 and 24, mean change in BCVA from Baseline to Month 12 and 24, the change in area of geographic atrophy at Month 12, the change in CRT from Baseline to Month 12 and Month 24, IRF and SRF at Months 2, 12 and 24, the proportion of patients gaining more than 15 letters or losing less than 15 letters from Baseline to Month 12 and Month 24 and the number of times a participant needed to return to monthly treatments during the 24 months.

All variables will be summarised by time point and treatment group using descriptive statistics. Full details of allocation of assessments to time points will be provided in the SAP. All data will be listed.

9.5.1.1 Visual acuity

The model to analyse BCVA will be an expansion of the model used to analyse BCVA from Baseline to 12 months for the 12 month data analysis.

A mixed model will be fitted with BCVA at each visit as the outcome variable and treatment as a class variable. All results for BCVA will be included. Visit will be included as a class variable in order to estimate the mean BCVA at each time and an interaction term to determine if the mean BCVA at each time differs between treatments. The change in BCVA between Baseline and Month 12 or Month 24 for each treatment and the difference between ranibizumab and aflibercept will be obtained along with 95% confidence limits. Subject will be included as a random term and the repeated nature of the data modelled by fitting the appropriate correlation structure. Other factors may be included in the model, such as centre. The decision on the correlation structure and additional factors will be fully detailed in the SAP.

Ranibizumab will be found to be statistically significantly better at increasing BCVA if the change from Baseline is more than that for aflibercept and $p < 0.05$.

9.5.1.2 Injection Frequency

The number of injections over the 24 month period will be analysed in a similar fashion to that for the 12 month data analysis using a Poisson or Negative Binomial model as appropriate for count type data. The number of injections in the 24 months will be the outcome variable and treatment as a class variable. The length of time each subject is in the study up to their 24 month visit will be used as an offset variable. The injection frequency (per 24 months) and the difference between injection frequencies will be obtained for each treatment group along with the corresponding 95% confidence intervals and p-values. The model may be expanded to cater for other time points. Details will be provided in the SAP. All data will be listed.

9.5.1.3 Central Retinal Thickness

The mean change in CRT from Baseline to Month 24 will be analysed as described for visual acuity above. All data will be listed.

9.5.1.4 Newly Developed Geographic Atrophy at 12 Months

A mixed model will be fitted as for the primary endpoint. In addition, a model fitting the development of geographic atrophy in the first 12 month period or the second 12 month period may be fitted to provide one analysis of the newly developed GA over time. This analysis would be undertaken using the method of generalised estimating equations. Full details will be provided in the SAP.

9.5.1.5 Proportion of patients showing no intraretinal and subretinal fluid at 2, 12 and 24 months

At each assessment the patient is examined for the presence/absence of IRF and SRF as per the definitions for their treatment arm (5.5.4.1). The number (and percentage) of patients in category (present/absent) for each assessment (IRF, SRF) will be presented by treatment group at each time point.

The presence/ absence of IRF classification of each patient at each timepoint will be modelled using logistic regression. Output will include prespecified comparisons of proportions between treatments at each visit and between treatments over all visits. A similar approach will be used for the presence/absence of SRF. Full details of the approach will be provided in the SAP.

All data will be listed.

9.5.1.6 Proportion of patients showing greater than 15 letters (logMAR) gain and less than 15 letters loss from Baseline to Months 12 and 24

The patient's BCVA at Month 12 (or the closest visit to Month 12) and Month 24 (or the closest visit to Month 24) will be compared with the baseline assessment. Patients will be classified as having >15 letters improvement (i.e. Month 12/24 – Baseline >15) or otherwise. The percentage of patients in each category at each timepoint will be presented by treatment group. A generalised estimating equation model will be fitted as described above for IRF.

Patients will also be classified as having a ≤ 15 letters loss or otherwise at each visit with the responses modelled using the generalised estimating equations approach.

9.5.1.7 Plasma VEGF

Blood for plasma VEGF is being collected at Baseline and again at 7 days after the injection at Week 4 (Visit 3) and 7 days after the injection at Week 8 (Visit 4). Descriptive statistics will be used to summarise plasma VEGF at these time points.

The concentration of VEGF will be compared between treatments using the mixed model approach as described for BCVA. All data will be listed.

9.5.1.8 Retinal nerve fibre analysis

Retinal nerve fibre analysis will be undertaken at Baseline and Month 24. All data will be listed. The proportion of patients with retinal nerve fibre damage will be provided by visit and treatment. Shift tables will present the change in nerve fibre status.

9.5.1.9 Safety variables

Safety parameters will include adverse events, the results of ophthalmic examinations, IOP, vital signs, and laboratory results if reported as AE, in addition to post-injection ocular inflammation at baseline and 7 days post-injection following 3rd mandated intravitreal injection.

All safety analyses will be conducted within 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 together with all other adverse events. Pre-treatment and treatment-emergent adverse events will be summarised separately.

Adverse events will be summarised by presenting for each treatment group the number and percentage of patients having any adverse event, having a study-eye-related adverse event, having a fellow-eye 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 experience multiple adverse events for a preferred term will be counted once, similarly for patients with multiple adverse events per system organ class.

All the AEs after the first on-study treatment will be listed with relation to the date of the study treatment.

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, summarised by primary system organ class and preferred term.

Vital signs and special tests

Vital signs will be summarised by presenting shift tables using extended normal ranges with thresholds representing clinical relevant abnormality and by presenting descriptive statistics of raw data and change from baseline. Values outside the extended normal 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).

Ocular inflammation is being assessed at Baseline and 7 days post the third injection and will be summarised using descriptive statistics only. The proportion of patients with each grade of inflammation will be presented by treatment group for each visit. Shift tables will present the change in inflammation status between visits by treatment group. All results will be listed.

9.6 12 Month Data Analysis

One analysis is planned at 12 months for the key secondary endpoints of the number of injections and mean change in BCVA from Baseline to Month 12. The rationale for this analysis of the key secondary endpoints is outlined in 3.5.

No power analysis was undertaken directly for the 12 month data analysis. However, the sample size estimated for the primary endpoint was assessed as to its adequacy for addressing the question of injection frequency at 12 months.

Assuming the 2-sided test for percentage developing geographic atrophy and a sample size of 121 per group, the sample size is also suitable for detecting a difference in injection frequency between ranibizumab and aflibercept at 12 months of:

- 0.7 injections if the standard deviation is 2,
- 0.9 injections if the standard deviation is 2.5
- 1.1 injections if the standard deviation is 3.0, and
- 1.3 injections if the standard deviation is as large as 3.5.

Power is 80%, alpha is 0.05, test is a two-sided t-test and no adjustment has been made to alpha, the type I error rate for assessing multiple endpoints. These assumptions are based on the CATT study (Martin et al, 2012).

The mean number of injections over the first 12 month period will be analysed using a Poisson or Negative Binomial model as appropriate for count type data. The number of injections in the first 12 months will be the outcome variable and treatment as a class variable. The length of time each subject is in the study up to their 12 month visit will be used as an offset variable. The injection frequency (per year) and the difference between injection frequencies will be obtained for each treatment group along with the corresponding 95% confidence intervals and p-values. The model may be expanded to cater for other time points once the study is completed. Details will be provided in the SAP.

The model to analyse mean change in BCVA from Baseline to 12 months will be a mixed model with BCVA at each visit as the outcome variable and treatment as a class variable. All results for BCVA from Baseline to Month 12 will be included. Visit will be included as a class variable in order to estimate the mean BCVA at each time and an interaction term to determine if the mean BCVA at each time differs between treatments. The change in BCVA between baseline and month 12 for each treatment and the difference between ranibizumab and aflibercept will be obtained along with 95% confidence limits. Subject will be included as

a random term and the repeated nature of the data modelled by fitting the appropriate covariance/correlation structure. Other factors may be included in the model, such as centre. The decision on the correlation structure and additional factors will be fully detailed in the SAP.

Ranibizumab will be found to be statistically significantly better at increasing BCVA if the change from Baseline is more than that for aflibercept and p <0.05.All data will be listed.

9.7 Sample size calculation

The sample size for the difference in the change in area of patients developing geographic atrophy is based on a two-sided z-test with α=0.05 and 80% power. Ranibizumab will be assessed against aflibercept and considered superior if the p-value for the z-test is <0.05 and the mean area of geographic atrophy is less for those on ranibizumab. A 95% two sided confidence interval for the difference in means will also be estimated. This is based on an assumption that a meaningful difference to detect is 20%. 278 patients should be able to detect a 20% difference in geographic area between the two groups based on expected change in Geographic Atrophy of 2mm/year with a sigma of 1.5.

9.8 Power analysis of key secondary variables

The key secondary variables are those addressed in the 12 month data analysis section above and the power of these analyses is addressed there.

No other power analyses were undertaken for any other secondary endpoints.

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 Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed Consent Procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative 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 IRB/IEC and a

copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the foetus 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.

10.3 Responsibilities of the Investigator and IRB/IEC

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

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. In addition, upon study completion and finalisation of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

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. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

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 IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient

included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

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