NOVARTIS

Clinical Development

RFB002/ranibizumab / NCT02130024

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

End of Study deliverables

Detailed Statistical Methodology

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SAP Approval

By my signature, I confirm that this SAP has been reviewed and approved for use on the CRFB002AAU17 study (End of Study deliverables):

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List of tables and figures

List of abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
AMD	Acute Macular Degeneration
APTC	Antiplatelet Trialists' Collaboration
ATE	Arterial Thromboembolic Event
BCVA	Best Corrected Visual Acuity
CI	Confidence Interval
CNV	Choroidal Neovascularisation
CRC	Central Reading Center
eCRF	electronic Case Report Form
GA	Geographic Atrophy
IOP	Intraocular Pressure
IRF	Intra-Retinal Fluid
LOCF	Last Observation Carried Forward
logMAR	Logarithmic Minimum Angle of Resolution
OCT	Optical Coherence Tomography
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SE	Standard Error
SRF	Sub-Retinal Fluid
VA	Visual Acuity

1 Introduction

The purpose of this document is to outline the statistical analyses planned for End of Study (EOS) deliverables. This document will also include 12 month interim analysis. The accompanying mock shells, will be compiled at a later date, prior to EOS data base lock.

[redacted]

Studies covered are listed in Table 1-1. The study design, objective, treatment duration, and efficacy variables for this indication may be different from other related studies due to different indications and phases of clinical development so that almost every study is unique. The main purpose is to provide project-level standards for the statistical analyses of efficacy and safety data which are common or similar across studies. This MAP can be used as a reference or guidance of statistical methods for future studies not listed in Table 1-1.

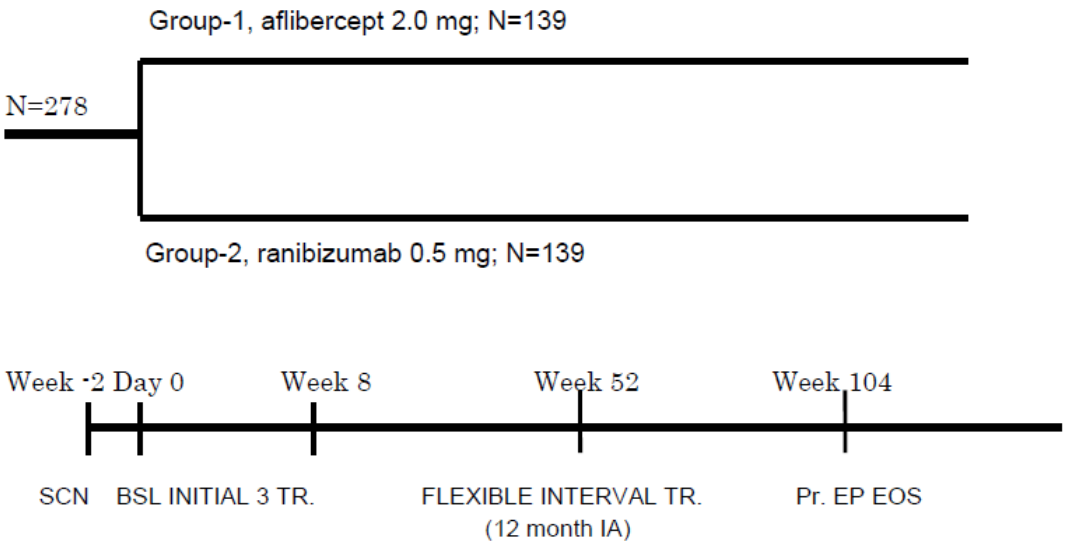
Table 1-1 Studies covered in the MAP

Indication /Study	Phase/ Duration	Treatment/ dose	Primary objective
AMD / RFB002	IV/ 24 Month	(1) Aflibercept/ 2.0 mg (2) Ranibizumab/ 0.5 mg	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 multimodal imagining assessed by an independent reading centre masked to the treatment arms).

This is a randomized, 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 randomized 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.

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 Interim analysis.

2 Project standards

Treatment groups for the analysis

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

2.1 General considerations

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.

The study eye is the eye identified by the investigator according to the protocol inclusion and exclusion criteria and recorded as such at the screening or Baseline visit in the electronic Case Report Form (eCRF).

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

For non-ocular, study eye, and fellow eye summary tables, figures, and listings will be based on all patients included in the analysis/set population under consideration. Unless otherwise specified, all confidence intervals (CIs) and p values will be two-sided and will be based on an alpha significance level of 0.05.

2.1 Analysis sets

The following are common analysis sets used across the project.

Randomized Set: The Randomized Set will consist of all randomized patients.

Full Analysis Set: The Full Analysis Set comprises all subjects randomized and who have at least one post-baseline efficacy value for the primary endpoint, defined as a Geographic Atrophy (GA) assessment as captured in the eCRF from Autofluorescence for the study eye. Following the intent-to-treat principle, subjects will be analysed according to the treatment regimen they were assigned to at randomization.

Safety Set: 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.

Per-Protocol Set: The Per-Protocol Set will consist of all patients in the Full Analysis Set who followed the treatment regimen as randomized without clinically significant protocol deviations. Clinically significant protocol deviations will be identified and documented prior to the database lock. Refer to "Protocol Deviations" study document for further details. [3]

In order to derive the analysis set, protocol deviations (defined prior to DB lock; impact on analysis defined in this document) and non-protocol deviations (based on the definition of the analysis set/according to this document) need to be considered.

The protocol deviations are mainly used in excluding entire patients or particular data within a patient from the Per-Protocol Set and are described in the Protocol Deviation Plan. Furthermore - to derive the analysis sets, non-protocol deviations will be used.

Table 2-1 Analysis set exclusion summary below gives a summary of the non-protocol deviations that exclude patients from each analysis set.

Table 2-1 Analysis set exclusion summary

Analysis Set (to be excluded from)	Non-Protocol Deviations
Full Analysis Set	Not in the Randomized set
	Did not record at least one post-baseline efficacy value for the primary endpoint (see details above)
Per-Protocol Set	Not in Full Analysis Set
	Clinically significant protocol deviation(s)
Safety Set	Did not receive at least one application of study treatment
	Did not record at least one post-baseline safety assessment

All efficacy evaluations will be carried out on the Full Analysis Set. The analysis for the primary efficacy evaluation will be carried out on both the Full Analysis Set and the Per-

Protocol Set. Analyses for secondary [redacted] evaluations will be carried out on the Full Analysis Set, and may also be carried out on the Per-Protocol Set as part of sensitivity analyses.

All safety evaluations will be carried out on the Safety set. Within the safety set, patients will be analysed as treated.

The number and percentage of patients in each analysis set will be summarized based on all randomized patients in the analysis set.

In addition, a listing will be produced to show the patient inclusion/exclusion into each of the analysis sets with the corresponding reason(s) for exclusion.

Note that additional analysis sets may be derived as part of sensitivity analyses.

2.2 Subgroup definitions

Sub-groups analyses may be included in [redacted] sensitivity analyses. Potential sub-groups:

- Randomization 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.
- Baseline Best Corrected Visual Acuity (BCVA)
- Baseline choroidal neovascularisation (CNV) lesion size
- Baseline CNV lesion type
- Baseline IRF and/or SRF

Sub-group analyses may include descriptive analyses as well as forest plot(s) displaying treatment effects within each sub-group.

2.3 Assessment windows, baseline and post baseline definitions, missing data handling

Assessment windows to be applied to this study are detailed in Table 2.3-3.

Table 2.3-3 Study Assessment Windows

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 Discontinuation
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

n = number of visits as required per study protocol section 5.5.4.1
v = variable. The number of visits will differ dependent on treatment interval as per study protocol section 5.5.4.1
†= 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.

2.3.1 Baseline and post-baseline definitions:

2.3.1.1 Baseline

Baseline is defined as the last available non-missing value collected just prior to the start of treatment in the study eye.

Where a patient parameter value is missing for Visit 2:

1. If the patient has entered the treatment period (i.e. received at least one treatment), the Baseline value for that patient will be imputed with the patient's Screening value.
2. If the patient never entered the treatment period, the Baseline value will not be imputed.

Furthermore, patients with screening assessments, who do not enter the treatment period data, will only be included in data listings.

Note:

If Baseline images i.e. Fluorescein Angiography, Autofluorescence, Optical Coherence Tomography (OCT), Colour Fundus - are missing or not of a sufficient quality for analysis, images from either Week 4 or Week 8 will be used as the baseline measurement.

2.3.1.2 Post-baseline

All assessments obtained after the date of first dose of study drug are considered as post-baseline unless otherwise specified. Missing data for post-baseline values, for example due to discontinuation, loss to follow-up, or other types of censoring (e.g. due to rescue medication), will not be imputed. Only subjects with measurements at any given time point will be included in the analysis for that given parameter and visit. Refer to Section 2.3.3 for further details regarding the handling of missing dates.

The study day for a Baseline or post-baseline scheduled or unscheduled visit is defined as:

Study day = (Date of visit) - (date of First Dosing) + 1

The study day for a scheduled or unscheduled visit before baseline is defined as:

Study day = (Date of visit) - (date of First Dosing).

Note: The first dosing day will be calculated as study day 1 according to CDISC standards. However, the protocol documented the first dosing day as Day 0.

2.3.1.3 Visit Windows

Data listings presented by visit will use the eCRF nominal visit windows (using planned visit dates), as well as the derived visit window (calculated using the actual visit date). Visit names available will be 4-weekly for the first 12 weeks, and then fortnightly. For example: Week 4, Week 8, Week 12, Week 14, Week 16, Week 18, etc...

For derived visit windows: the actual post-baseline visit's study day (as determined in 2.3.1.2) will be allocated to a derived visit window as follows:

- Week 4: if the actual visit's study day is between Day 2 (inclusive) and Day 43 (inclusive);

- Week 8: if the actual visit's study day is between Day 44 (inclusive) to Day 71 (inclusive);
- Week 12: if the actual visit's study day is between Day 72 (inclusive) to Day 92 (inclusive);
- Week 14, Week 16, etc.: if the actual visit's study day is within ([Actual date's Week number x 7] ± 7 days)+1, exclusive at lower bound and inclusive at upper bound.

Any other outputs requiring presentation by visit (e.g. tables) will use eCRF nominal visit windows, unless specified otherwise in the respective sections of the SAP.

2.3.1.4 Early Discontinuation

Early Discontinuation visits will be assigned to a derived visit window based on the date of termination. If the Early Discontinuation visit is assigned to a visit window that already exists, then the assigned visit number will be set to the next visit window.

In data listings presented by visit, an Early Discontinuation visit will be labelled both as per the eCRF nominal visit number (i.e. "End of Study/M24") and as per the corresponding derived visit number, as described above.

Early Discontinuation visits may also be summarized as a separate distinct visit, in addition to, or in place of, the approach described in the paragraph above.

There will be no imputation for missing data in the primary analysis of the primary and secondary endpoints for those patients who discontinued the study early. For supporting and sensitivity analysis of the primary endpoint, 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.

Sensitivity analyses may be conducted to assess the impact of possible biases in endpoint analyses due to missing endpoint data for early withdrawal patients. These analyses may include Last Observation Carried Forward (LOCF), Baseline Observation Carried Forward (BOCF) and other imputation methods, as detailed further in Section 2.7.2.2.

2.3.2 Study observation period

The study observation period for each patient will be defined as the period (in days) between the date of first treatment in the study eye (Day 1) and the date of the end of study visit + 1 (day).

2.3.3 Missing and implausible dates

The general approach to handling missing dates is shown below for dates of Adverse Events (AEs), medical history diagnosis and concomitant treatment.

2.3.3.1 Adverse event start date imputation

AEs with completely missing onset dates will be considered to be treatment emergent. Adverse events with partially missing onset dates will also be included as treatment emergent when the month (if it exists) and the year occur on or later than the month and year of the initial study treatment date.

Partial AE start dates are imputed with reference to the treatment start date (TRTSTD) as outlined in the Imputation table below. Completely missing start dates will not be imputed.

For individual data listings, any missing or partial AE start dates will always be presented as recorded.

The date value is split into day, month, year sections and referenced in the Imputation table as outlined below:

	Day	**Month**	**Year**
Partial AE Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Comparison of Month Section	**MON MISSING**	**MON<TRTM**	**MON=TRTM**	**MON>TRTM**
YYYY MISSING	NC	NC	NC	NC
YYYY<TRTY	(D)=01JULYYY Before Treatment Start	(C)=15MONYYYY Before Treatment Start	(C)=15MONYYYY Before Treatment Start	(C)=15MONYYYY Before Treatment Start
YYYY=TRTY	(B)=TRTSTD+1 Uncertain	(C)=15MONYYYY Before Treatment Start	(A)=TRTSTD+1 Uncertain	(A)=01MONYYYY After Treatment Start
YYYY=TRTY	(E)=01JANYYYY After Treatment Start	(A)=01MONYYYY After Treatment Start	(A)=01MONYYYY After Treatment Start	(A)=01MONYYYY After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment Start	Partial date indicates AE start date prior to Treatment Start Date
After Treatment Start	Partial date indicates AE start date after Treatment Start Date
Uncertain	Partial date insufficient to determine relationship of AE start date to Treatment Start Date
Imputation Calculation	
NC / Blank Uncertain	No convention
(A) After Treatment Start or Uncertain	MAX(01MONYYYY,TRTSTD+1)
(B) Uncertain	TRTSTD+1

(C) Before Treatment Start	15MONYYYY
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

2.3.3.2 Medical history date of diagnosis imputation

Completely missing dates will not be imputed. Partial dates of diagnosis will be compared to the treatment start date.

- If DIAG year < treatment start date year and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY)
    - else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY)
- If DIAG year = treatment start date year
    - and (DIAG month is missing OR DIAG month is equal to treatment start month), the imputed DIAG date is set to one day before treatment start date
    - else if DIAG month < treatment start month, the imputed DIAG date is set to the midmonth point (15MON YYYY)
    - else if DIAG month > treatment start month => data error
- If DIAG year > treatment start date year => data error

2.3.3.3 Concomitant treatment date imputation

In order to classify a medication as prior or prior/concomitant, it may be necessary to impute the start date. Concomitant treatments with partial start dates will have the date or dates imputed. Partial concomitant treatment start dates are imputed with reference to the treatment start date (TRTSTD) in accordance with the rules outlined below:

Concomitant treatments with completely missing start dates will not be imputed. As a conservative approach, such treatments will be classified as prior/concomitant (i.e. as being received on or after the start of study treatment).

	Day	**Month**	**Year**
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Comparison of Month Section	MON MISSING	MON<TRTM	MON=TRTM	MON>TRTM
YYYY MISSING	(C) Uncertain	(C) Uncertain	(C) Uncertain	(C) Uncertain
YYYY<TRTY	(D)=01JULYYY Before Treatment Start	(A)=15MONYYYY Before Treatment Start	(A)=15MONYYYY Before Treatment Start	(A)=15MONYYYY Before Treatment Start
YYYY=TRTY	(C) Uncertain	(A)=15MONYYYY Before Treatment Start	(C) Uncertain	(B)=01MONYYYY After Treatment Start
YYYY=TRTY	(E)=01JANYYYY After Treatment Start	(B)=01MONYYYY After Treatment Start	(B)=01MONYYYY After Treatment Start	(B)=01MONYYYY After Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Treatment Start	Partial date indicates CMD start date prior to Treatment Start Date
After Treatment Start	Partial date indicates CMD start date after Treatment Start Date
Uncertain	Partial date insufficient to determine relationship of CMD start date to Treatment Start Date
Imputation Calculation	
NC / Blank Uncertain	No convention
(A) Before Treatment Start	15MONYYYY
(B) After Treatment Start	MAX(01MONYYYY,TRTSTD+1)
(C) Uncertain	IF CMDTYP1C IN (1, 3) THEN TRTSTD-1 ELSE IF CMDTYP1C IN (. 2) THEN TRTSTD+1
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

2.4 Subject disposition, background and demographic characteristics

2.4.1 Subject disposition

The number of subjects randomized and included in each of the analysis sets will be presented by treatment group. The number and percentage of subjects in the Randomized Set who

completed the study, who discontinued the study and the reason for discontinuation will be presented for each treatment group and for all subjects (Total).

The number of subjects screened only will also be presented. In addition, the reasons for screen failures will be provided.

2.4.2 Protocol deviations

All clinically significant protocol deviations will be summarized by number and percentage of patients with each deviation. Patients with multiple protocol deviations will only be counted once at each level of summarization. In addition, a listing of protocol deviations will be produced including the date and study day of the deviation occurrence with the accompanying deviation details. Deviations will be summarized for the Full Analysis Set. Refer to the protocol deviation plan for the Protocol Deviations / non-Protocol Deviations) defined for this study.

Note that protocol deviations may lead to exclusion of data based on a per-patient, per-visit or per-variable basis, as described in the protocol deviation plan.

2.4.3 Background and demographic characteristics

The following background and demographic variables will be analysed using the Randomized Set:

Continuous variables (**as per eCRF**):

- Age (years)

Categorical variables (**as per eCRF**):

- Gender (Male, Female)
- Race (Caucasian, Black African, Asian, Aboriginal and Torres Strait Islander, Pacific Islander, Other, Not sure)
- Ethnicity (Anglo Saxon, Northern European, Southern European, Asian Indian, Other, Not sure)

For continuous variables, descriptive statistics (mean, median, standard deviation, minimum and maximum) will be presented for each treatment group and for all subjects (Total).

For categorical variables, the number and percentage of subjects in each category will be presented for categorical variables for each treatment group and for all subjects (Total).

2.4.4 Eligibility

All eligibility data, including inclusion and exclusion criteria, will be listed.

2.4.5 Baseline Characteristics

The following Baseline characteristic variables will be analysed using the Randomized Set:

Categorical Baseline variables (**as per eCRF**):

- Study eye selection (L/R)
- Prior wet AMD treatment for fellow eye (Yes/No)
- Prior wet AMD Treatment (Lucentis, Eylea, Visudyne, Avastin, Steroids, Other)
- Family history of AMD

- History of arterial thromboembolic events
- Smoking history ("Never smoked", "Current smoker", "Smoked in the past")

Continuous Baseline efficacy variables:

- Total BCVA score (**as per eCRF**)
- GA assessments (**as per Central Reading Centre**)
  - Area of GA (mm^2, Can't grade, NA), as measured on Autofluorescence*
  - Longest linear dimension (μm), as measured on OCT
- OCT assessments (**as per Central Reading Centre**):
  - Central subfield foveal thickness (CSFT) (The mean thickness values measured in 1mm diameter between the internal limited membrane layer and the bruch's membrane)
  - Subfoveal choroidal thickness (central Subfoveal choroidal thickness)
  - Nerve Fibre analysis (Mean thickness of the retinal nerve fibre layer on a circle scan of the optic nerve head)
- Fluorescein Angiography assessments (**as per Central Reading Centre**):
  - Area of lesion (mm^2)
  - Area of active CNV (mm^2)

Categorical Baseline efficacy variables:

- Visual acuity >=70 letters (20/40) – **as per eCRF**
- Visual acuity <70 letters – **as per eCRF**
- GA assessments (**as per Central Reading Centre**)*
  - Presence on Color Fundus Photography (Present, Absent, Can't grade)
  - Presence on Fluorescein Angiography (Present, Absent, Can't grade)
  - Presence on OCT (Present, Absent, Can't grade)
  - Present on Autofluorescence (Present, Absent, Can't grade)
  - Overall determination of GA presence (Yes, No)*
  - Location of GA on Autofluorescence (N/A, Can't grade, Central subfield, Inner subfield, Outer subfield), if overall determination of GA is present
- GA – **as per eCRF**
  - If present, Linear dimension (≤ 249 μm, ≥ 250 μm)
- OCT assessments (**as per Central Reading Centre**):
  - Intra-retinal fluid (Present, Absent, Can't grade)
    - Intra-retinal fluid center involvement (Present, Absent, Can't grade) [If IRF = present]
  - Sub-retinal fluid (Present, Absent, Can't grade)
    - Sub-retinal fluid center involvement (Present, Absent, Can't grade) [If SRF = present]
  - PED (Present, Absent, Can't grade. Solid, Hollow, Mixed. Subfoveal: Yes/No. If yes, max height within 1mm diameter)

  - Vitreoretinal Abnormalities (Present, Absent, Can't grade. If present: Epiretinal membrane [if affecting fovea], vitreomacular adhesion, vitreomacular traction, macular hole, other)
  - Subretinal hyper reflective material (Present, Absent)
- Fluorescein Angiography assessments (**as per Central Reading Centre**):
  - Evidence of CNV complex (lesion), Study Eye Only (Present, Absent, Can't grade)
  - CNV leakage (Present, Absent)
  - Type of CNV (predominantly classic, minimally classic/occult, RAP lesion, Can't grade, other)
  - CNV complex (lesion) location, Study Eye only (subfoveal, juxtafoveal, extrafoveal, Can't grade)
  - Lesion components (CNV, Blood, Serous PED, RPE rip/tear, Can't grade, Blockade, other)
- Colour fundus assessments (**as per Central Reading Centre**):
  - Presence of Retinal Haemorrhage (Yes, No) (**also as per eCRF**)
  - AMD abnormality (drusen, hemorrhages, atrophy, fibrosis, PED, Pigmentary changes) (Present, Absent, Can't grade)
- Autofluorescence assessments (**as per Central Reading Centre**):
  - Evidence of Hyperfluorescence (Present, Absent, Can't Grade)
  - Hyperfluorescence Type (Focal, Banded, Diffuse)
  - Evidence of Reticular Pseudodrusen – subretinal deposits (Present, Absent, Can't Grade)
  - Evidence of RPE rip/tear (Present, Absent, Can't Grade).

* GA will be determined as present or absent based on definitions in the current Central Reading Centre Study Specification Worksheet. If deemed present, GA area will also be measured. Diagnosis of GA was confirmed if it is present in two of the imaging modalities, one of which had to be OCT or Autofluorescence.

Note for the study 12-month interim analysis: no data was extracted from the Central Reading Centre. The only structural data to be described in the interim analysis were the CNV location and the CNV classification at baseline, as reported in the eCRF.

Summary statistics will be presented for each treatment group and for all subjects (Total) in the Randomized Set, for all Baseline characteristics (including the Baseline values of the main efficacy endpoints).

For continuous variables, descriptive statistics will be presented.

For categorical variables, the number and percentage of subjects in each category will be presented for each treatment group and all subjects (Total).

2.4.6 Medical history

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 (Version 17). Separate tables will be provided for ocular (study eye and fellow eye) and ATE histories

and conditions. The number and percentage of subjects with each medical condition will be provided by treatment group for the Randomized Set.

Additionally, all information will be listed including the investigator reported term, and the diagnosis/surgery date.

2.5 Study medication

2.5.1 Exposure

The following summaries will be presented for the injections in the study eye using the Safety Set:

- The number and percentage of patients receiving study medication by treatment group and visit.
- Duration of Exposure
    - Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be presented using days as the unit.
- The number of injections presented by treatment group in frequency tables by visit and cumulatively. The output will be presented by visit based on eCRF nominal visit windows, and may also be presented by visit based on derived visit windows.

2.5.2 Treatment patterns

The following summaries of treatment patterns over 12 and 24 Months will be presented using the Full Analysis Set:

- Treatment frequency
- Total number of injections
- Reason for interval decision (as defined within disease activity for each arm)
- The interval between treatments (the first, second and third intervals extensions)
- The number of times patients return to monthly treatments.

The number of injections administered per patient for injections in the study eye will be summarized. Both the frequency distribution (number of patients with 1 injection, number of patients with 2 injections, and so on up to the maximum number of injections for any one patient for the given treatment period) and summary statistics for the number of injections per patient will be presented.

Injections administered on, or after, the Month 12 visit, will count towards the 2nd year of treatment.

The listing containing information on dose administration in the study eye, will also include total number of injections in the study eye.

2.6 Prior and Concomitant medication

The number and percentage of patients taking concomitant therapies will be summarized by preferred term according to the WHO Drug Reference List dictionary (September 2013) using the Safety Set. Summaries will be presented over two time periods, in separate tables: therapies received prior to the start of study treatment and therapies received after the start of study treatment. Categorization of the time period will be determined based on recorded or imputed start and end dates of medications. Rules for imputing incomplete (start and end) dates are described in Section 2.3.3.3.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Chemical (ATC) codes and Preferred Terms. Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular Anatomical Therapeutic Chemical code and at least one drug in a particular anatomical main group.

For concomitant medication, a separate summary will be provided for ocular (location of the condition treated).

2.7 Efficacy evaluation

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 autofluorescence images assessed by an independent masked reading centre), based on square root transformed data (which decreases the dependency of GA growth on baseline GA size). Supportive and Sensitivity analyses will be conducted as described in Section 02.

Other key secondary variables include the number of injections from Baseline to Month 12 and the mean change in BCVA (logMAR) from Baseline to Month 12.

2.7.1 Variables

The primary efficacy variable and key secondary variables are:

- The mean change in area of geographic atrophy from Baseline to Month 24
- The number of injections from Baseline to Month 12
- The mean change in BCVA (logMAR) from Baseline to Month 12.

The remaining secondary variables (efficacy and safety) are:

- The mean change in area of existing and newly developed geographic atrophy from Baseline to Month 12
- The proportion of patients showing new 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 subfield foveal thickness 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 (Present/Absent)
- Proportion of patients showing greater than and equal to a 15 letters (logMAR) gain from Baseline to Month 12 and 24
- The proportion of patients showing less 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.

2.7.2 Statistical hypothesis, model, and method of analysis

Statistical methodologies for efficacy variables are detailed in Table 2.7.2-1 (Primary and Key Secondary efficacy) and Table 2.7.2-2 (Secondary efficacy).

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 change in area of geographic atrophy, based on square root transformed data, is less than that for aflibercept.

Table 2.7.2-1 Primary and Key Secondary Efficacy Analyses

Study Endpoint	Method of Analysis
Primary: Mean change in area of geographic atrophy in the study eye from Baseline to Month 24, based on square root transformed data.	1. Mixed Modelling (Refer to Section 2.7.2.5) 2. Summary statistics of change from Baseline will be presented.
Key Secondary: Number of injections from Baseline to Month 12	1. Negative Binomial Regression Model (Refer to Section 2.7.2.7)
Key Secondary: Mean change in BCVA (logMAR) from Baseline to Month 12	1 Mixed Modelling (Refer to Section 2.7.2.5) 2. Summary statistics of change from Baseline will be presented.

Table 2.7.2-2 Remaining Secondary Efficacy Analyses

Study Endpoint	Method of Analysis
Mean change in area of geographic atrophy in the study eye from Baseline to Month 12.	1. Mixed Modelling (Refer to Section 2.7.2.85)
The proportion of patients with no GA at baseline who developed new geographic atrophy by Month 12 **The proportion of patients with no GA at Month 12 who developed new geographic atrophy by Month 24**	1.Logistic Regression Model (Refer to Section 2.7.2.8)
The number of injections from Baseline to Month 24	1. Negative Binomial Model (Refer to Section 2.7.2.7)
The mean change in BCVA (logMAR) from Baseline to Month 24	1.Mixed Modelling (Refer to Section 2.7.2.5) 2. Summary statistics of change from Baseline will be presented
The mean change in central subfield foveal thickness from Baseline to Months 12 and 24	1.Mixed Modelling (Refer to Section 2.7.2.85) 2. Summary statistics of change from Baseline will be presented
The proportion of patients showing no intraretinal fluid (IRF) and subretinal fluid (SRF) at Months 2, 12 and 24 (Present/Absent)	1.Logistic Regression Model (Refer to Section 2.7.2.8)
The proportion of patients showing greater than and equal to a 15 letters (logMAR) gain from Baseline to Months 12 and 24	1. Logistic regression model (Refer to Section 2.7.2.8)
The proportion of patients showing less than and equal to a 15 letters (logMAR) loss from Baseline to Months 12 and 24	1. Logistic regression model (Refer to Section 2.7.2.8)
Plasma VEGF concentrations	1.Mixed Modelling (Refer to Section 2.7.2.85) 2. Summary statistics will be presented by time points

2.7.2.1 Descriptive Summaries

All data will be listed.

All continuous data will be summarized by mandatory scheduled visit time point and treatment group using descriptive statistics, unless otherwise stated in the SAP. All categorical data will be summarized by mandatory scheduled visit time point (if appropriate) and treatment group by the number (and percentage) of patients in each category, unless otherwise stated in the SAP.

NOTE: certain outputs, presented by visit, may in addition use derived visit windows.

2.7.2.2 Supportive/Sensitivity Analyses

1. The primary endpoint will be assessed using a mixed model (as described in 2.7.2.5) with no imputation for missing data, using the Full Analysis Set.

   As a supporting analysis, the primary model will also be fitted to the Per-Protocol Set.

   Sensitivity analyses may be carried out by re-fitting the model with missing data imputed (as detailed further in Section 2.7.2.3) using:

   - Last Observation Carried Forward (LOCF) in the following way:
     - Mixed model (as described above)
     - A cross-sectional analysis at Month 24 by using an ANCOVA model.
   - Non-transformed GA size (data provided by the Central Reading Centre)
     - Mixed model (as described above)
     - A cross-sectional analysis at Month 24 by using an ANCOVA model.
   - Multiple imputation.
   - The main analysis is based on a random effects mixed model (subject specific model). Different correlation structure between the repeated measured data could be considered. Therefore, a mixed model for repeated measures (MMRM, marginal model) could be used to assess the robustness of the conclusion based on the main analysis. In the MMRM, the variance-covariance structure of the repeated measures will be specified as 'Unstructured'.

2. Key secondary endpoints will be analysed with no imputation for missing data. As a supporting analysis, the key secondary endpoint models may also be fitted to the Per-Protocol Set.

   For the mean change in BCVA from Baseline to Month 12 (interim analysis at Month 12), a sensitivity analyses may be conducted with missing data imputed using the LOCF imputation method (mixed model) and may be analysed cross-sectionally by an ANCOVA model and multiple imputation.

3. The remaining secondary endpoints will be analysed with no imputation for missing data. In addition, the remaining secondary endpoint models may be fitted to the Per-Protocol Set as a supporting analysis. Sensitivity analyses may be conducted; including the re-fitting of models with missing data imputed using the LOCF and multiple imputation.

2.7.2.3 Handling of missing values/discontinuations in efficacy analyses

For the primary analysis there will be no imputation for missing data. For supporting and sensitivity analysis, the area of GA at the last on-study visit will be used for patients who withdraw prior to the 12 or 24 month visit.

The mixed model approach where all values at mandatory scheduled visits recorded for each patient up to the time of study completion (or withdrawal) are used, is an appropriate model for data missing at random.

Sensitivity analyses will be conducted to explore the robustness of the data to the methods of dealing with missing data. These methods will include LOCF and multiple imputation, as applicable.

2.7.2.4 Center pooling

Not Applicable

2.7.2.5 Mixed Modelling

The mixed models to be fitted are detailed in Table 2.7.2.5-1.

Table 2.7.2.5-1 Mixed Models

Model Number	Outcome Variable	Covariate/Predictor		Class Variable		Random Term
		Definite	Optional	Definite	Optional	
MM_1	Change in area of geographic atrophy in the study eye from Baseline to Months 12 and 24, based on square root transformed data.	• Baseline Area of GA in study eye (continuous) • Treatment • Visit (categorical) • Treatment by Visit interaction	At Baseline: • Presence of any GA in fellow eye (Y/N) • Presence of any GA in study eye (Y/N) • Location of GA in study eye (categorical: central subfield, inner subfield, outer subfield) • Presence of IRF in study eye (Y/N) • Presence of SRF in study eye (Y/N) • BCVA (continuous) • Presence of Reticular Pseudodrusen in study eye (Y/N) • Presence of Reticular Pseudodrusen in fellow eye (Y/N) • Area of active CNV (continuous) • CNV lesion type (categorical: classic, minimally classic/occult, RAP) • Age (continuous) • Subfoveal choroidal thickness (continuous)	Treatment Visit Subject	Stratum Center	Subject

			• Presence of Retinal Haemorrhage (per CRC) (Y/N) [Note: AMD abnormalities = present] • Presence of Epiretinal Membrane (ERM) OCT (Y/N) [Note: AMD abnormalities = present] ***May also be carried out if deemed relevant:*** *Baseline:* • *Past history of smoking (Y/N)* • *Any treatment ever given to the fellow eye prior to Screening? (Y/N)* • *Presence of Pigment Epithelium Detachment on OCT (Y/N)* • *Presence of Subretinal hyperreflective material on OCT (Y/N)*			
MM_2	Change in BCVA (logMAR) from Baseline to Months 12 and 24	• Baseline BCVA (continuous) • Treatment • Visit (categorical) • Treatment by Visit interaction	<u>Baseline</u>: • Presence of IRF in study eye (Y/N) • Presence of SRF in study eye (Y/N) • Presence of Fibrosis in study eye (Y/N) • Presence of subfoveal GA in study eye (Y/N) [Note: Overall determination of GA presence = Yes and Location of GA central subfield = Yes] • Age (continuous) • Area of active CNV (continuous) • CNV Lesion type (categorical: categorical: classic, minimally classic/occult, RAP) ***May also be carried out if deemed relevant:*** *Baseline:* • Area of lesion (continuous)	Treatment Visit Subject	Stratum Center	Subject

MM_3	Change in central subfield foveal thickness from Baseline to Months 12 and 24	• Baseline central subfield foveal thickness (continuous) • Treatment • Visit (categorical) • Treatment by Visit interaction	Baseline: • Presence of IRF in study eye (Y/N) • Presence of SRF in study eye (Y/N) • Presence of Fibrosis in study eye (Y/N) • Presence of subfoveal GA in study eye (Y/N) [Note: Overall determination of GA presence = Yes and Location of GA central subfield = Yes] • Age (continuous) • Area of active CNV (continuous) • CNV Lesion type (categorical: classic, minimally classic/occult, RAP)	Treatment Visit Subject	Stratum Center	Subject
MM_4	Plasma VEGF concentrations at Weeks 5 and 9	• Baseline plasma VEGF concentrations (continuous) • Treatment • Visit (categorical) • Treatment by Visit interaction	Baseline: • Bilateral treatment (categorical)	Treatment Visit Subject	Stratum Center	Subject

Results from mandatory visits will be included for each model, unless otherwise indicated. The repeated nature of the data will be modelled by including subject as random effect. The Kenward-Roger (KR) correction will be used to compute the denominator degrees of freedom to test fixed effects. The least square (LS) mean estimate for "Ranibizumab"treatment group – "Aflibercept"treatment group will be obtained where treatment time = 24 Months and where treatment time = 12 Months, as appropriate. These will be obtained with 95% confidence limits.

In regards to the BCVA key secondary endpoint, ranibizumab will be found to be statistically significantly better at increasing BCVA if the change from Baseline is more than that for aflibercept and $p < 0.05$.

2.7.2.6 Generalised Estimating Equations

In addition, a model fitting the development of new 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. New geographic atrophy is defined as the change in diagnosis of GA from "No" to "Yes". This analysis would be undertaken using a Generalised Estimating Equation logistic regression. The General Estimating Equations analysis includes repeatedly collected GA data from different visits into one model, and the correlation of the repeatedly collected data is accounted for by the model.

Absence/Presence of IRF and/or SRF may also be analysed using a Generalised Estimating Equation logistic regression at Months 2, 12 and 24.

2.7.2.7 Analysis of Binomial Data

The mean 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 Negative Binomial model for count type data. The number of injections in the 24 Months will be the outcome variable and treatment as a class variable. The logarithmic 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 12 months) and the difference between injection frequencies (ratio) 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.

2.7.2.8 Logistic regression

The logistic regression models to be fitted are detailed in Table 2.7.2.8-1.

Table 2.7.2.8-1 Logistic Regression Models

Model Number	Outcome Variable	Predictor/Covariate	
		Mandatory	Optional
LR_1	The proportion of patients with no GA at baseline who developed new* GA by Month 12 (Yes/No) The proportion of patients with no GA at Month 12 who developed new* GA by Month 24 (Yes/No)	Treatment	Center Baseline: Presence of GA in the **fellow eye** (Y/N) CNV Lesion type (categorical: classic, minimally classic/occult, RAP) Presence of IRF in study eye (Y/N) Presence of SRF in study eye (Y/N) Presence of Reticular Pseudodrusen in study eye (Y/N) BCVA (continuous) Age (continuous) Area of active CNV (continuous) Subfoveal choroidal thickness (continuous)
LR_2	Proportion of patients with no intraretinal fluid (IRF) and subretinal fluid (SRF) at Months 2, 12 and 24	Treatment	Center Baseline: Presence of IRF/SRF in study eye BCVA (continuous) Area of lesion (continuous) Area of active CNV (continuous)
LR_3	Proportion of patients showing ≥15 letters gain from Baseline to Months 12, 24 (Yes/No)	Treatment	Center Baseline BCVA (continuous)

LR_4	Proportion of patients showing ≤15 letters loss from Baseline to Months 12, 24 (Yes/No)	Treatment	Center Baseline BCVA (continuous)

* New GA is defined as diagnosis of GA change from "No" to "Yes", as determined by the Central Reading Center using multimodal imaging (overall determination of GA presence).

From each model the adjusted odds ratio for the outcome variable, for ranibizumab compared with aflibercept, will be obtained with 2-sided 95% confidence limits.

Using PROC GENMOD to calculate the 95% confidence interval for the odds ratios assumes asymptotic normality of the Wald estimate for the regression coefficient. The 95% confidence interval for the regression parameter of ranibizumab treatment effect relative to aflibercept is calculated using an exponential transformation to create the 95% confidence interval for the odds ratio.

All p-values reported on linear hypotheses about regression coefficients will be based on the Wald tests from Type III analyses. In the SAS procedure PROC GENMOD, a Type III analysis will be performed by adding the model options: TYPE3, DIST=BIN, and LINK=LOGIT.

The repeated binary data for absence/presence of IRF and/or SRF may also be assessed using a random intercept logistic regression (under the frame work of generalized linear mixed model) with robust estimation of standard error (SE).

2.7.2.9 Time to Event

Time to **newly** developed GA will be analysed by survival analysis. Kaplan-Meier survival function will be summarized and plotted. Cox proportional hazards model may also be used as deemed appropriate. The **newly** developed GA is defined as any reported post baseline GA for those subjects without GA at baseline. Subjects without **newly** developed GA will be censored at the last visit date or withdrawal date, whichever occurs first.

2.8 Safety evaluation

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.

2.8.1 Adverse events

Adverse events (AEs) will be reported by primary system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.

AEs will be deemed treatment emergent if the onset date is on or after the date of first study treatment. Any AEs recorded prior to the start of study treatment will be listed together with all other AEs. Pre-treatment and treatment-emergent adverse events will be summarized separately. If any event has an incomplete onset date, this will be handled as described in section 2.3.3.1 above.

The incidence of treatment emergent AEs will be summarized separately for ocular AEs as follows:

- All AEs
- AEs by maximum severity
- AEs suspected to be related to study drug
- Serious AEs
- AEs leading to study treatment discontinuation

In addition, arterial thromboembolic events (ATEs) will be summarized, including: overall ATEs and APTC ATEs.

Patients who experienced multiple adverse events for a preferred term will be counted once, similarly for patients with multiple adverse events per system organ class.

All information pertaining to AEs noted during the study will be listed by patient, detailing AE (e.g., verbatim given by the investigator as well as the system organ class and preferred term according to MedDRA), date of starting and ending, severity, suspected relationship (by the investigator) to the study drug / ocular injection, and eye (for ocular events). The AE onset will also be shown relative (in number of days) to the day of (first) initial study treatment and relative (in number of days) to the Day 1.

The following AE listings will be provided:

- All adverse events
- Ocular adverse events
- Adverse events suspected to be related to study drug and/or ocular injection
- Serious adverse events
- Adverse events leading to treatment withdrawal
- Adverse events leading to treatment interruption.

2.8.2 Laboratory data

No laboratory evaluations to assess blood or urine parameters will be performed – with the exception of pregnancy assessments, if applicable.

2.8.3 Vital signs

Vital signs will be listed with values outside the extended normal range flagged as: H (High) and L (Low).

Vital signs (sitting systolic and diastolic blood pressure (mmHg)) will be summarized by treatment group using descriptive statistics for all time points assessed, including change from Baseline for all post-Baseline assessments. Shift tables from Baseline to all post-Baseline assessments will also be generated for each parameter with values of Within Normal Limits (WNL), High, and Low used for the shift categories.

Categories for “High” and “Low” are defined as follows:

- High
    - Systolic (mmHg): either >180 with increase from Baseline >30 or >200 absolute
    - Diastolic (mmHg): either >105 with increase from Baseline >20 or >115 absolute;

- Low
    - Systolic (mmHg): either <90 with decrease from Baseline >30 or <75 absolute
    - Diastolic (mmHg): either <50 with decrease from Baseline >20 or <40 absolute.

2.8.4 Electrocardiogram (ECG)

No ECG performed during this study.

2.8.5 Intra-Ocular Pressure (IOP)

IOP measurements will be summarized by treatment group, for the study eye, using descriptive statistics for all time points assessed, including change from Baseline for all post-Baseline assessments.

2.8.6 Ophthalmologic Examination

Ophthalmic examination results for the study and fellow eye will be listed separately and will include:

- Cornea (Normal, Abnormal)
- Iris (Normal, Abnormal)
- Vitreous (Normal, Abnormal)
- Disc (Normal, Abnormal)
- Retina other than wAMD (Normal, Abnormal)
- Lens (Phakic, Aphakic, Pseudophakic)
- AREDS grading; 1st, 2nd and 3rd criteria (Nuclear Sclerosis, Cortical, PSC)
- Grade categorised as (<2='none to mild' or >2='moderate to severe').

In addition, ophthalmic examination results will be summarized by treatment group, for the study eye, using descriptive statistics.

2.8.7 Retinal nerve fibre analysis at Baseline and Month 24

Retinal nerve fibre analysis will be undertaken at Baseline and Month 24. 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.

Categories for "Decrease", "No Change" and "Increase" are defined as follows:

- Decrease (i.e. a decrease of >10 μm from Baseline)
- No change (i.e. within ±10 μm from Baseline)
- Increase (i.e. an increase of >10 μm from Baseline).

2.8.8 Ocular Inflammation

Ocular inflammation is being assessed at Baseline and 7 days post the third injection and will be summarized using descriptive statistics. 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.

2.8.9 Meta-analysis

Not Applicable.

2.9 Interim analyses (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. AEs (Adverse Events) and SAEs (Serious Adverse Events) may be included descriptively.

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 Negative Binomial model 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 logarithmic 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 (ratio) between injection frequencies will be obtained for each treatment group along with the corresponding 95% confidence intervals (CI) and p-values.

The model to analyse mean change in BCVA from Baseline to 12 Months will be a random effects mixed model. In the random effects mixed model, change in BCVA from Baseline at Week 4, Week 8 and Month 12 (mandatory visits) will be included in the model as the outcome (response) variable and treatment as a class variable. Visit will be included as a class variable in order to estimate the mean BCVA change from Baseline at Week 4, Week 8 and Month 12 and an interaction term to determine if the mean BCVA change from Baseline at Week 4, Week 8 and Month 12 differs between treatments. The model will also include baseline BCVA as a continuous variable for the purpose of baseline covariate adjustment. The change in BCVA between Baseline and Month 12 for each treatment and the difference between ranibizumab and aflibercept (least square (LS) mean estimate for "Ranibizumab"treatment group – "Aflibercept"treatment group) will be obtained along with 95% confidence limits. The repeated nature of the data will be modelled by including subject as random effect. The Kenward-Roger (KR) correction will be

used to compute the denominator degrees of freedom to test fixed effects. Other factors may be included in the model, such as centre.

The 12 Month pre-planned interim analysis was conducted for information purposes only, with no stopping rule set up at interim analysis.

2.10 Data monitoring committee (DMC)

Not Applicable.

2.11 Sample size and power considerations

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 (also see Section 2.9 Interim Analyses).

2.12 Pharmacokinetic analyses

Not applicable.

3 References

1.Clinical Study Protocol, Version 02, dated 19 January 2015.

2.eCRF, Version 3.0, dated 04 November 2014.

3. CRFB002AAU17 Protocol Deviation Plan Version 1 04 Jul 2014.

4. CRFB002AAU17 SSW V5 23 Jun 2016.