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Clinical Development

RFB002/ranibizumab / NCT01972789

A Phase IV, randomised, controlled, single masked study investigating the efficacy and safety of ranibizumab "inject and extend" using an intensive retinal fluid retreatment regimen compared to a relaxed retinal fluid retreatment regimen in patients with wet age-related macular degeneration (AMD).

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 CRFB002AAU15 study:

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1 Introduction

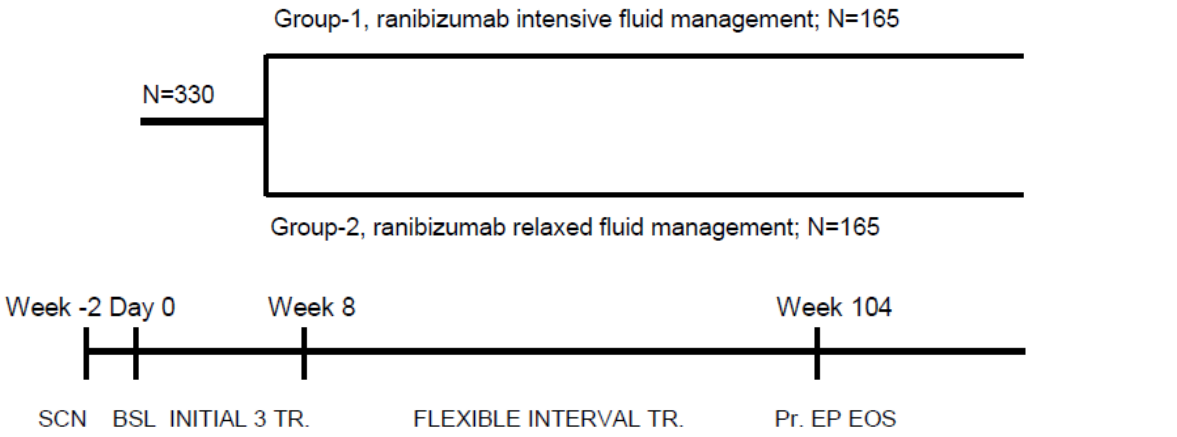
Studies covered are listed in Table 1-1. The study design, objective, treatment duration, and efficacy variables for this indication may be different from other related studies due to different indications and phases of clinical development so that almost every study is unique. The main purpose is to 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	(1) Intensive retinal fluid retreatment regimen (2) Relaxed retinal fluid retreatment regimen	To test the non-inferiority (visual acuity benefit that is not clinically worse) of intravitreal ranibizumab when administered to resolve IRF or SRF >200 μm under the fovea (relaxed retinal fluid management) relative to when administered to completely resolve both IRF and SRF (intensive retinal fluid management) in patients with wet AMD. The primary endpoint for the study will be the mean change in BCVA from baseline to month 24.

This is a randomised, multi-centre, non-inferiority trial investigating a relaxed fluid retreatment regimen relative to an intensive fluid retreatment regimen (using a non-inferiority margin of 5 letters on the primary endpoint of mean change in BCVA). 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. intensive retinal fluid regimen or relaxed retinal fluid regimen 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.

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.



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.

Figure 1 Study design

2 Project standards

Treatment groups for the analysis

The group labels for the 2 treatment groups for the analysis are: “Intensive” (Group I) and “Relaxed” (Group II).

2.1 General considerations

Descriptive statistics will include n (number of observations), mean, standard deviation, median, minimum and maximum for continuous variables, and frequencies and percentages for categorical variables.

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 visit in the eCRF.

The efficacy analyses of this study will be based on the study eye data only.

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.

Central Reading Centre data will be used for efficacy summary tables and analyses, whilst all site and Central Reading Centre data will be included in listings.

2.2 Analysis sets

The following are common analysis sets used across the project.

Randomized Set: The Randomised Population will consist of all randomised patients.

Full Analysis Set (FAS): The Full Analysis Set (FAS) compromises all subjects randomised and whom have at least one post-baseline efficacy value for BCVA.

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.

Per-Protocol Set: 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. Refer to "Protocol Deviations" study document for further details.[1]

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 (PPS) 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 have at least one post-baseline efficacy value for BCVA
Per Protocol Set	Not in FAS
	Clinically significant protocol deviation(s)
Safety Set	Did not receive at least one study treatment
	Did not record at least one post-baseline safety assessment

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. Analyses for secondary and exploratory evaluations will be carried out on the FAS, and may also be carried out on the PPS population as part of sensitivity analyses. Within the FAS and PPS, patients will be analysed as randomised.

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 patients included 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.

2.3 Subgroup definitions

Sub-groups analyses may be included in exploratory and sensitivity analyses. Potential sub-groups:

- Randomisation Strata: Two treatment naïve eyes, one eye (first non-study eye) being treated with ranibizumab, and one eye (first non-study eye) being treated with an anti-VEGF other than ranibizumab.
- Age Group
- Sex
- Baseline BCVA group (>=70 letters, <70 letters)
- Genotype sampling status
- Baseline lesion size
- 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.

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

Assessment windows to be applied to this study are detailed in Table 2.4-3.

Table 2.4-3 Study Assessment Windows

Period	Screen	Initial Treatment			Treatment Period			
Visit	**1**	**2**	**3**	**4**	**n**	**Month 12**	**n**	**Month 24 or Early Discontinuation**
Weeks (relative to Baseline, Day 0)	-2 to 0	Baseline	4	8	v	52	v	104
Visit window (days)			±3	±3	±7	± 14	± 7	±14

n = number of visits as required per study protocol[2] section 5.5.4.1
v = variable. The number of visits will differ dependent on treatment interval as per study protocol[3] section 5.5.4.1

2.4.1 Baseline and post-baseline definitions:

2.4.1.1 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: Photography and FA performed no more than 14 days before the Baseline Visit will be accepted as the baseline examination (will not need to be repeated unless clinically indicated).

Note: BCVA performed no more than 2 days before the Baseline Visit will be accepted as the baseline examination. In addition, only BCVA data collected as per protocol (e.g. refracted ETDRS) will be accepted as the baseline examination.

2.4.1.2 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 2.4.3 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 treatment) + 1

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

Study day = (Date of visit) - (date of first treatment)

2.4.1.3 Visit Windows

Output presented by visit will use a derived visit number, based on the number of weeks from Day 1; the derived visit number will be calculated using the actual visit date, as opposed to the scheduled visit date. Listings will also include the CRF nominal visit.

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., with each visit having a visit window of ± 7 days.

Month 12 and Month 24 visits will be analysed using the CRF nominal visit window.

2.4.1.4 Early Discontinuation

The standard approach to handling Early Discontinuation visits will be to assign the visit to a derived visit number based on the date of termination. If the Early Discontinuation visit is assigned to a visit which already exists, then the assigned visit number will be set to the next visit.

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

In addition, 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 2.8.2.2.

2.4.2 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).

2.4.3 Missing and implausible dates

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

2.4.3.1 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

2.4.3.2 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

2.4.3.3 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

2.5 Subject disposition, background and demographic characteristics

2.5.1 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 Full Analysis Set (FAS) who completed the study, who discontinued the study and the reason for discontinuation will be presented for each treatment group and all subjects.

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

An additional table will summarise and compare the number of subjects randomized by treatment group and site.

2.5.2 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 code and severity. Deviations will be summarized for the Randomized Set. Refer to the protocol deviation plan for the PDs / non-PDs 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.

2.5.3 Background and demographic characteristics

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

Continuous variables (per eCRF):

- Age (years)

Categorical variables (per eCRF):

- Gender (Male, Female)
- Race, grouped as
  - Caucasian: Afghan, Caucasian, Egypt, Egyptian, El Salvadore, Greek, Hispanic, Israeli, Italian, Maltese, Middle East, Middle Eastern, South American, Turkish, Yugoslavian
  - Black African
  - Asian: Asian and Indian;
  - Aboriginal and Torres Strait Islander
  - Pacific Islander
  - Not sure
- Ethnicity (Anglo Saxon, Northern European, Southern European, Asian Indian, Other)

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 all subjects (total). The number and percentage of subjects with missing data will also be presented.

2.5.4 Eligibility

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

2.5.5 Baseline Characteristics

The following baseline characteristic variables will be analysed using the Randomised Set:

Categorical baseline variables (per eCRF):

- Study eye selection (L/R)
- Prior wet AMD treatment for fellow eye (Yes/No)
- Prior wet AMD treatment for fellow eye (Lucentis, Eylea, Visudyne, Avastin, Steroids, Other)
- Family history of AMD
- History of thromboembolic events
- Smoking history (as reported, as well as grouped with “Never smoked” and “Smoked in the past” combined)

Continuous baseline efficacy variables:

- Total BCVA score (per eCRF)
- OCT assessments (per [redacted]):
  - Central subfield foveal thickness (CSFT) (μm^2)
  - Central subfield volume (mm^3)
- FA assessments (per [redacted]):
  - Area of lesion (mm^2)
  - Area of CNV (mm^2)
  - Area of Geographic atrophy (mm^2)

Categorical baseline efficacy variables

- Visual acuity >=70 letters (20/40) - per eCRF
- Visual acuity <70 letters – per eCRF
- OCT assessments (per [redacted]):
  - Intra-retinal fluid (Present, Absent, Can't grade) (within 6x6mm scan) (also per eCRF)
  - Intra-retinal fluid centre involvement (Present, Absent, Can't grade)
  - Intra-retinal cysts (Present, Absent)
  - Intra-retinal cysts centre involvement (Present, Absent)
  - Sub-retinal fluid (Present, Absent, Can't grade) (within 6x6mm scan) (also per eCRF)
  - Sub-retinal fluid centre involvement (Present, Absent, Can't grade) (within 6x6mm scan)
  - Sub-retinal fluid at centrepoint (Present, Absent, Can't grade)
  - Sub-retinal fluid height at centrepoint (>200um, ≤200um, not applicable) (also per eCRF)
  - Morphologic changes (epiretinal membrane, vitreoretinal traction, macular hole, atrophy, other)

- FA assessments (per [redacted]):
  - CNV complex (lesion) (Absent, Definite, Questionable etc.) (also per eCRF)
  - CNV complex (lesion) location (subfoveal, juxtafoveal, extrafoveal, can't grade)
  - CNV complex (lesion) location (subfoveal, juxtafoveal, extrafoveal, can't grade), by presence of fluid central involvement
  - CNV location (subfoveal, juxtafoveal, extrafoveal, can't grade) (also per eCRF)
  - CNV location (subfoveal, juxtafoveal, extrafoveal, can't grade), by presence of fluid central involvement
  - CNV secondary to (AMD, angioid streaks, idiopathic, pathologic myopia, other)
  - Type of CNV (predominantly class, occult, fibrovascular PED, serous PED, other
  - CNV leakage (Present, Absent)
  - Lesion components (CNV, blood, serous PED, RPE tear, can't grade, other)
  - Geographic atrophy (Absent, Definite, Can't grade etc.)
  - Geographic atrophy location (central subfield, inner subfield, outer subfield)

- Colour fundus assessments (per [redacted]):
  - Haemorrhage (Absent, definite, Can't grade, NA)
  - Haemorrhage location (central subfield, inner subfield, outer subfield)
  - Retinal abnormality (drusen, atrophy, fibrosis, PED, other) (Present, Absent)
  - Retinal abnormality location (central, periphery)

Summary statistics will be presented for each treatment group and for all subjects (total) in the Randomised 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 categorical variables for each treatment group and all subjects (total). The number and percentage of subjects with missing data will also be presented.

An analysis will be conducted to compare baseline age, visual acuity, lesion size, SRF and IRF between those participants who provided a saliva sample and those who did not.

Study Endpoint	**Method of Analysis**
Comparison of baseline visual acuity between participants who provided a genotyping saliva sample and those who did not	Mixed Model
Comparison of baseline SRF between participants who provided a genotyping saliva sample and those who did not	Logistic regression model
Comparison of baseline IRF between participants who provided a genotyping saliva sample and those who did not	Logistic regression model
Comparison of age between participants who provided a genotyping saliva sample and those who did not	Mixed Model
Comparison of lesion size between participants who provided a genotyping saliva sample and those who did not	Mixed Model

The mixed model analyses will include genotype saliva sample status as a definite class variable and treatment group as an optional class variable. Further details regarding the general mixed model approach are detailed in Section 2.8.2.5.

Logistic Regression analyses will include genotype saliva sample status as the predictor variable. Further details regarding the general logistic regression approach are detailed in Section 2.8.2.5.

2.5.6 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. Separate tables will be provided for ocular (study eye and fellow eye) and non-ocular histories and conditions. The number and percentage of subjects with each medical condition will be provided by treatment group for the Randomised Set.

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

2.6 Study medication

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

- Duration of Exposure
    - Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be presented using days as the unit.
- The number of ranibizumab injections presented by treatment group in frequency tables by visit and cumulatively.

Analyses of the treatment exposure and treatment patterns of the two alternative treatment regimens over 24 months include:

- Treatment frequency
- Total number of injections
- Reason for interval decision (as defined within disease activity for each arm)

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, 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.

Additionally, a listing of summarized dosing parameters (e.g., total number of injections in the study eye) will be provided. A listing will also be provided detailing data related to the study observation period.

Furthermore, to assess visit/treatment frequency and average visit/dosing interval, the following summaries will be provided (within the FAS)

- The number (%) of patients by the maximum visit interval (4, 6, 8, 10 and 12 weeks); a visit interval is defined as the difference of the visit week number as from the visit date. E.g. if the first visit to be considered is recorded as Week 16 visit and the next visit is recorded as Week 22 visit, then the visit interval is 6 weeks; the maximum visit interval is evaluated on a patient level, i.e. the longest visit interval within the study for each patient.

- The number (%) of patients for whom the visit interval was never decreased, decreased once, decreased two times; The decrease of the visit interval is based on a comparison with the previous visit interval. E.g. if the previous visit interval was 8 weeks and the current visit interval is 6 weeks (4 weeks), then the visit interval was decreased by 2 weeks (4 weeks).
- The number (%) of patients by breakpoint interval (4, 6, 8, 10 and 12 weeks); (the injection interval equals the visit interval)
- The number (%) of patients by the number of times the patient returned to monthly injections.
- The number (%) of patients with presence of new haemorrhage, fluid (SRF, IRF) or a loss of visual acuity of ≥5 letters related to study indication, by visit and disease activity (over all post-baseline visits).
- The number (%) of patients with presence of vision impairment attributable to disease activity related to study indication, by visit (over all post-baseline visits).
- The number of scheduled and attended post-baseline visits by patients will be summarized (i.e. all scheduled and attended visits after baseline).
- The number of injections by patients will be summarized. Injections administered on, or after, the Month 12 visit, will count towards the 2nd year of treatment.
- The average time (in days) between visits scheduled for treatment will be summarized; the time "delta" between 2 consecutive visits will be calculated as: delta = (Date of visit x) - (date of visit x-1) + 1; the average per patients will then be summarized.

2.7 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 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. Categorisation 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 2.4.3.3.

Medications will be presented in alphabetical order, by ATC codes and grouped by *anatomical main group* (the 1st level of the ATC codes). Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

For both prior and concomitant medications, separate summaries will be provided for non-ocular, study eye, and fellow eye. Treatments that are specified as being taken in both eyes will be included in summaries for both the study eye and the fellow eye.

2.8 Efficacy evaluation

The primary objective is to evaluate the effectiveness of two treatment regimens by assessing the mean change in BCVA from baseline to Month 24 in each treatment group. A key secondary endpoint is to evaluate the effectiveness of two treatment regimens by assessing the mean change in BCVA from baseline to Month 12 in each treatment group. A mixed model (see below) utilising all data will be the primary analysis to assess both these endpoints in the one analysis with no imputation for missing data. Supportive and Sensitivity analyses will be conducted as described in Section 2.8.2.1.

Other key secondary variables include the central retina thickness and number of injections at Month 12 and Month 24.

2.8.1 Variables

The primary efficacy variable and key secondary variables are:

- Mean change in BCVA from baseline to month 24
- Mean change in BCVA from baseline to month 12
- Mean change in central retinal thickness from baseline to month 12 and month 24
- Number of injections from baseline to month 12 and 24

The additional secondary variables are:

- Mean change in area of new and existing geographic atrophy from baseline to month 12 and 24.

  Patients at sites where autofluoresence can be undertaken will be assessed for the presence of geographic atrophy at Baseline, visit 4 (week 8) and then again at the 12 and 24 month visits. If present, the area of geographic atrophy will be estimated.

  - New Geographic Atrophy at month 12 and month 24[a] (Yes, No)
  - Change in area of geographic atrophy from the visit where geographic atrophy was first present

- Intra-retinal (IRF) and Sub-retinal fluid (SRF) (present/absent)

  At each relevant assessment visit, the patient is examined for the presence/absence of IRF and SRF by the central reading centre as per the definitions for their treatment arm.

- The proportion of patients showing no IRF and SRF at month 2, 12 and 24
- Proportion of patients showing greater than or equal to 15 letters (EDTRS) gain and less than 15 letters loss from baseline to month 24.
- Proportion of patients with SRF as assessed by the [redacted] CRC and IRF as assessed by Investigators at baseline who do not resolve their SRF and IRF by Month 24

The remaining exploratory variables are:

- Proportion of patients with a) SRF, b) IRF, c) both SRF and IRF, d) neither SRF and/or IRF at baseline, month 2, 12 and 24
- Proportion of patients with ≥6/12 visual acuity at baseline, month 12 and month 24
- Proportion of patients with 6/60 or worse visual acuity at baseline, month 12 and 24
- The proportion of patients with IRF and SRF at baseline who never resolve either their IRF or SRF at any visit up to Month 2, 12 and 24.
- Proportion of patients with SRF at baseline who never resolve their SRF at any visit up to Month 2, 12 and 24 (irrespective of their IRF)
- Proportion of patients with IRF at baseline who never resolve their IRF at any visit up to Month 2, 12 and 24 (irrespective of SRF)

2.8.2 Statistical hypothesis, model, and method of analysis

Statistical methodologies for efficacy variables are detailed in Table 2.8.2-1 (Primary efficacy), Table 2.8.2-2 (Secondary efficacy) and Table 2.8.2-3 (Exploratory efficacy).

Table 2.8.2-1 Primary and Key Secondary Efficacy Analyses

Study Endpoint	Method of Analysis
Mean change in BCVA from baseline to months 12 and 24	1. Mixed Modelling (Refer to Section 2.8.2.5) 2. Summary statistics of change from baseline will be presented.
Mean change in central retinal thickness (CRT) from baseline to months 12 and 24	1. Mixed Modelling (Refer to Section 2.8.2.5) 2. Summary statistics of change from baseline will be presented.
Mean number of injections from baseline to months 12 and 24	1. Binomial Model 2. All data will be listed.

Table 2.8.2-2 Additional Secondary Efficacy Analyses

Study Endpoint	Method of Analysis
Geographic Atrophy from Baseline to Month 12 / 24 (newly developed geographic atrophy between baseline and Month 24 (Yes/No))	1. Logistic regression model (Refer to Section 2.8.2.8) 2. Survival Analysis (Refer to Section 2.8.2.10)
Geographic Atrophy from Baseline to Month 12 / 24 (Change in area of geographic atrophy from the visit where geographic atrophy was first present)	1. Mixed Modelling (Refer to Section 2.8.2.8)
Proportion of patients showing greater than or equal to 15 letters (EDTRS) gain from baseline to month 24	1. Logistic regression model (Refer to Section 2.8.2.8)
Proportion of patients showing less than 15 letters loss from baseline to month 24	1. Logistic regression model (Refer to Section 2.8.2.8)
Proportion of patients showing no IRF and SRF at month 2, 12 and 24	1. Logistic regression model (Refer to Section 2.8.2.8)

Table 2.8.2-3 Exploratory Efficacy Analyses

Study Endpoint	Method of Analysis
Proportion of patients with SRF, as assessed by the [redacted] CRC, and IRF, as assessed by investigators at Baseline, who do not resolve their SRF and IRF by Month 24	1. Logistic regression model (Refer to Section 2.8.2.8)
The proportion of patients with a) SRF b) IRF c) both SRF and IRF d) neither SRF or IRF at baseline, 2, 12, 24 months	1. Logistic regression model (Refer to Section 2.8.2.8)

Proportion of patients with SRF at baseline who never resolve their SRF at any visit up to Month 2, 12 and 24 (irrespective of their IRF)	1. Logistic regression model (Refer to Section 2.8.2.8)
Proportion of patients with IRF at baseline who never resolve their IRF at any visit up to Month 2, 12 and 24 (irrespective of SRF)	1. Logistic regression model (Refer to Section 2.8.2.8)
Proportion of patients with IRF and SRF at baseline who never resolve either their IRF or SRF at any visit up to Month 2, 12 and 24.	1. Logistic regression model (Refer to Section 2.8.2.8)
Proportion of patients who show ≥6/12 visual acuity at baseline, month 12 and 24	1. Logistic regression model (Refer to Section 2.8.2.8)
Proportion of patients who show 6/60 or worse visual acuity at baseline, month 12 and 24	1. Logistic regression model (Refer to Section 2.8.2.8)
Time to Breakpoint	1. Kaplan Meier Survival Analysis (Refer to Section 2.8.2.10)

2.8.2.1 Descriptive Summaries

All data will be listed.

All continuous data will be summarised by timepoint and treatment group using descriptive statistics. All categorical data will be summarized by timepoint (if appropriate) and treatment group by the number (and percentage) of patients in category.

For all patients, data will be recorded on scheduled visits for treatment. These visits are based on a bi-weekly visit grid, however each patient has their own set of scheduled visits which are determined by disease activity/visual impairment. Therefore, the number of visits differs between patients and as a consequence the number of available assessments/data at each visit differs. The time course of efficacy variable data will be presented/summarized as per the observed scheduled visits. As this differs between patients “by visit” tables presenting the overall time-course will be based on a biweekly time-grid.

Endpoints for BCVA improvement or BCVA loss will be summarized by presenting the number and percentage of patients in each treatment achieving the endpoint.

The mean BCVA value will be presented graphically by time point and treatment group, categorized by baseline BCVA value. The baseline categories will be: -0.29-0.00, 0.01-0.30, 0.31-0.60, 0.61-0.90, 0.91-1.20 and 1.21-1.50. The same graph will be presented for the mean BCVA change from baseline.

2.8.2.2 Supportive/Sensitivity Analyses

The primary endpoint will be assessed using a mixed model as described above with no imputation for missing data. Sensitivity analyses may include re-fitting the model with missing data imputed using the LOCF and multiple imputation (as detailed further in Section 2.8.2.3).

In addition, the primary model will be fitted to the Per-Protocol Set as a supporting analysis. Secondary and exploratory models may also be fitted to the Per-Protocol set as supporting or sensitivity analyses.

Secondary endpoints will be assessed with no imputation for missing data. Sensitivity analyses may be conducted; including the re-fitting of models with missing data imputed using the LOCF and multiple imputation, if appropriate. Furthermore, the secondary endpoint models may be fitted to use the Per-Protocol Set as supporting analyses.

Statistical models with optional variables may be explored to identify which model(s) optimally fit the data. In addition, ANCOVAs may be used to confirm cross-sectional analyses, as applicable.

Furthermore, one of the secondary outcomes is to explore the percentage of patients with > 15 letter improvement. This analysis provides a further supporting analysis of the primary endpoint.

2.8.2.3 Handling of missing values/discontinuations in efficacy analyses

For the primary analysis, there will be no imputation for missing data. The mixed model approach where all values recorded for each patient up to the time of withdrawal (or completion) 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.

2.8.2.4 Centre pooling

Not Applicable

2.8.2.5 Mixed Modelling

The mixed models to be fitted are detailed in Table 2.8.2.5-1.

Table 2.8.2.5-1 Mixed Models

Model Number	Outcome Variable	Predictor/Covariate		Class Variable		Random Term
		Definite	Optional	Definite	Optional	
MM_1	Change in BCVA from baseline to 2, 12 and 24 months	• Treatment • Baseline BCVA • Visit (categorical) • Treatment by Visit Interaction	• Stratification group • Cumulative weeks on treatment	Treatment Visit Subject		Subject
MM_2	Change in BCVA from baseline to 2, 12 and 24 months	• Treatment • Baseline BCVA • Visit (categorical) • Treatment by Visit Interaction	• Injection frequency • Cumulative number of weeks on treatment • Stratification group <u>Baseline</u>: • Age • Lesion size • GA presence • Smoking status • Genotype saliva sample status • Baseline BCVA (<=70/>70) • Baseline IRF • IRF • Baseline SRF • SRF • PED • SRF resolved (y/n)	Treatment Visit Subject	Stratum Centre	Subject
MM_3	Change in Geographic Atrophy from baseline to 2, 12 and 24 months.	• Treatment • Baseline GA area • Visit (categorical) • Treatment by Visit Interaction	• Cumulative number of weeks on treatment Baseline: • Age • BCVA • Injection frequency • Lesion size • GA presence • Smoking status • Genotype saliva sample status • Baseline BCVA (<=70/>70) • Baseline IRF • IRF • Baseline SRF • SRF • PED • SRF resolved (y/n)	Treatment Visit Subject	Stratum Centre	Subject

Model Number	Outcome Variable	Predictor/Covariate		Class Variable		Random Term
		Definite	Optional	Definite	Optional	
MM_4	Change in CRT from baseline to 2, 12 and 24 months	• Treatment • Baseline CRT • Visit (categorical) • Treatment by Visit Interaction	• Injection frequency • Cumulative number of weeks on treatment • Stratification group Baseline: Age • Lesion size • GA presence • Smoking status • Genotype saliva sample status • Baseline BCVA (<=70/>70) • Baseline IRF • IRF • Baseline SRF • SRF • PED • SRF resolved (y/n)	Treatment Visit Subject	Stratum Centre	Subject

All results for all patients for 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 intensive retinal fluid treatment group ("intensive") – relaxed retinal fluid treatment group ("relaxed") will be obtained for treatment time = 2 months, 12 months and 24 months. These will be obtained with 95% confidence limits.

In regards to primary efficacy, if the upper 2-sided 95% confidence limit for the least square mean for intensive – relaxed mean change in BCVA at 24 months is <5 (the non-inferiority margin) then relaxed will be declared non-inferior to intensive.

2.8.2.6 Generalised Estimating Equations

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 a generalised estimating equation (GEE) logistic regression.

Absence/Presence of IRF and/or SRF may also be analysed using a GEE logistic regression.

2.8.2.7 Analysis of Binomial Data

The mean number of injections over the 24-month period will be analysed using a Negative Binomial model for count type data. The number of injections will be the outcome variable and treatment as a class variable. The logarithm 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 year) 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 such as 12 months or separate analyses.

2.8.2.8 Logistic regression

The logistic regression models to be fitted are detailed in Table 2.8.2.8-1.

Table 2.8.2.8-1 Logistic Regression Models

Model Number	Outcome Variable	Predictor/Covariate	
		Mandatory	Optional
LR_1	Newly developed geographic atrophy between baseline and Month 12 / 24 (Yes/No)	Treatment	Baseline geographic atrophy Baseline IRF/SRF Centre
LR_2	≥ 15 letter increase from baseline to month 24 (Yes/No)	Treatment	Baseline BCVA Centre
LR_3	SRF and IRF at baseline and never resolving SRF at any visit up to Month 2 (Yes/No) Same for Month 12 and 24	Treatment	Baseline IRF/SRF Centre
LR_4	Greater than or equal to 15 letters (EDTRS) gain and less than 15 letters loss from baseline to month 24	Treatment	Baseline BCVA Centre
LR_5	SRF as assessed by the [redacted] CRC and IRF as assessed by Investigators who do not resolve their SRF and IRF by Month 24	Treatment	Baseline IRF/SRF Centre
LR_6	No IRF and SRF at month 2, 12 and 24	Treatment	Baseline IRF/SRF Centre
LR_7	SRF (as assessed by the [redacted] CRC) and IRF (as assessed by Investigators) who do not resolve their SRF and IRF by Month 24	Treatment	Baseline IRF/SRF Centre
LR_8	IRF at baseline who never resolve their IRF at any visit up to Month 2, 12 and 24 (irrespective of SRF)	Treatment	Baseline IRF Centre

Model Number	Outcome Variable	Predictor/Covariate	
		Mandatory	Optional
LR_9	IRF and SRF at baseline who never resolve either their IRF or SRF at any visit up to Month 2, 12 and 24.	Treatment	Baseline IRF/SRF Centre
LR_10	Show ≥6/12 visual acuity at baseline, Month 2, Month 12, month 24	Treatment	Baseline BCVA Centre
LR_11	Show 6/60 visual acuity or worse at baseline, Month 2, Month 12, month 24	Treatment	Baseline BCVA Centre

From each model the adjusted odds ratio for the outcome variable, for intensive compared with relaxed treatment, 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 the relaxed regime treatment effect relative to the intensive regime 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 SE.

2.8.2.9 Genotyping

Exploratory models will be fitted to investigate the correlation between genotype expression and visual acuity and dry retina. Analyses relating to genotype expression will be planned in an independent Statistical Methods document, and will also be reported independently.

2.8.2.10 Time to Event

Time to event analyses will be conducted using Kaplan Meier. Cox Hazards analysis may also be used as deemed appropriate.

2.9 Safety evaluation

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

All safety analyses will be conducted within the Safety Set.

2.9.1 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).

The MedDRA version used for reporting the study will be described in a footnote.

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. If any event has an incomplete onset date, this will be handled as described in section 2.4.3.1 above.

The incidence of treatment emergent AEs will be summarized separately for ocular and non-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

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 (ranibizumab injection) 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

2.9.2 Laboratory data

No laboratory evaluations to assess blood or urine parameters will be performed – with the exception of pregnancy assessments as described in Section 2.5.5, and DNA genotyping as described in Section 2.8.

2.9.3 Vital signs

Vital signs will be listed with values outside the extended normal range flagged.

Vital signs (sitting systolic and diastolic blood pressure (mmHg)) will also be summarised.

2.9.4 Electrocardiogram (ECG)

No ECG performed during this study.

2.9.5 Intra-Ocular Pressure (IOP)

IOP measurements will be summarised by treatment group using descriptive of raw data and change from baseline.

Change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as described in Section 0.

2.9.6 Ophthalmologic Examination

Ophthalmic examination data 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 AMD (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')

2.9.7 Meta-analysis

Not Applicable

2.10 Interim analyses

There is no planned interim analysis.

2.11 Data monitoring committee (DMC)

An independent Data Monitoring Committee (DMC) will be used in this study for assessment of data at 6 monthly timepoints commencing after 50% patients have completed the Month 12 visit. The composure of and procedures applied by the DMC is outlined in the data monitoring committee charter.[4]

2.12 Sample size and power considerations

This study is designed as a non-inferiority trial. The non-inferiority limit for the difference between groups (change with intensive treatment – change with relaxed treatment) is 5.

Therefore, if the upper 2-sided 95% confidence limit for the difference between treatments (intensive – relaxed) in the change in BCVA (on treatment – baseline) is < 5 the relaxed treatment will be declared non-inferior to the intensive treatment.

Assuming a Standard Deviation (SD) of 15 (as used in the CATT study; Martin et al, 2012) and assuming no true difference between treatments, a sample size of 165 patients per group provides 80% power assuming analysis will be conducted using a t-test. The sample size of 165 per group (total of 330) will be randomised (this allows for 15% drop-out based on the CATT study which observed an 11% dropout in the ranibizumab as needed group and 16% in the bevacizumab as needed group over the two years in the study). Calculations were performed using SAS V9.3.

2.13 Pharmacokinetic analyses

Not applicable

3 Summary of Changes to Planned Analyses

3.1 Statistical Analysis Plan, Version 1.0, 9-April-2017

3.1.1 Additional baseline efficacy variables

Additional baseline efficacy variables added to baseline characteristics analysis.

Protocol: Not included

SAP: Section 2.5.5, added:

- Visual acuity >=70 letters (20/40) - per eCRF
- Visual acuity <70 letters – per eCRF

3.1.2 Additional baseline characteristics analysis

Baseline characteristics analysis added to compare baseline characteristics between subjects who did, and did not, provide saliva samples for genotypjng.

Protocol: Not included

SAP: Section 2.5.5, added:

> An analysis will be conducted to compare baseline age, visual acuity, lesion size, SRF and IRF between those participants who provided a saliva sample and those who did not.

3.1.3 Additional exploratory analyses added

Additional exploratory endpoints incorporated following review of recently published literature.

Protocol: Not included

SAP: Additional exploratory endpoints added in Section 2.8.1:

- Proportion of patients with a) SRF, b) IRF, c) both SRF and IRF, d) neither SRF and/or IRF at baseline, month 2, 12 and 24
- Proportion of patients with ≥6/12 visual acuity at baseline, month 12 and month 24
- Proportion of patients with 6/60 or worse visual acuity at baseline, month 12 and 24
- The proportion of patients with IRF and SRF at baseline who never resolve either their IRF or SRF at any visit up to Month 2, 12 and 24.

- Proportion of patients with SRF at baseline who never resolve their SRF at any visit up to Month 2, 12 and 24 (irrespective of their IRF)
- Proportion of patients with IRF at baseline who never resolve their IRF at any visit up to Month 2, 12 and 24 (irrespective of SRF)

4 References

[1] Protocol Deviations, RFB002 / CRFB002AAU15, V1, 21 November 2013.

[2] Clinical Study Protocol, RFB002 / CRFB002AAU15, V2, 11 February 2013.

[3] Clinical Study Protocol, RFB002 / CRFB002AAU15, V2, 11 February 2013.

[4] Data Monitoring Committee Charter, RFB002 / CRFB002AAU15, Version dated 18 December 2013.