NOVARTIS

Medical Division

Ranibizumab/Lucentis®

CRFB002EJP09 / NCT02953938

A 12-month, phase IV, open-label, randomiZed, actIve controlled, 2-arm, multiPle-center study Assessing the efficacy and safety of intravitreal raNibizumab combined with Grid&Direct short pulse laser photocoagulation versus a PRN Ranibizumab monotherapy in Japanese patients with macUlar edema secondary to branch retinal vein occlusion (BRVO): ZIPANGU study

Statistical Analysis Plan (SAP)

Author:	Trial Statistician, [redacted]

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
25-Nov-2016	Prior to DB lock	Creation of final version	N/A - First version	NA
20-Sep-2018	Before dry run activity	Updates [redacted]	Scatterplot of decimal BCVA with retinal sensitivity, [redacted]	Section 2.13.1, Section 2.4.1
			Scatterplot of total number of injections with retinal sensitivity, [redacted]	
			Flagging pateint level data for laser treatment exposure <0.02 and >0.03 as high and low.	
25-Feb-2019	After dry run activity and Prior to DB lock	Creation of Final amendment v 2. 0 based on updates [redacted]	Baseline definition	Section 2.1.1
			Screened set	Section 2.2
			Loss / Gain of visual acuity (VA) based on BCVA decimal, BCVA LogMAR and BCVA ETDRS letters	Section 2.7.2
			Categorized Change for BCVA LogMAR	Section 2.7.2
			Baseline ETDRS BCVA (<60 letters and >= 60 letters)	Section 2.7.5
			Laboratory data	Section 2.8.3
			Start Date Imputation	Section 5.1.3.1
			End Date Imputation	Section 5.1.3.2
			Visit Windows	Section 5.1.3.5
29-Mar-2019	After DB lock	Creation of Final addendum v 1.0 based on updates [redacted]	Baseline ETDRS BCVA (<58 letters and >= 58 letters)	Section 2.7.5

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Updated titles of Table 5.1-4 and Table 5.1-5 for severity code and Text	Section 5.5
			Replaced MTYPE Variable Name with TRTSTD	Section 5.1.3.1

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List of abbreviations

AE	Adverse event
BCVA	Best-corrected visual acuity
BRVO	Branch Retinal vein occlusion
BSL	Baseline
CF	Color fundus photography
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organization
CSFT	Central subfield thickness
CSR	Clinical Study report
DAR	Drug administration record
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
[redacted]	[redacted]
FAS	Full Analysis Set
IgG	Immunoglobulin G
IOP	Intraocular pressure
logMAR	Logarithmic minimum angle of resolution
[redacted]	[redacted]
ME	Macular edema
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRN	Pro re nata
PRO	Patient-reported Outcomes
[redacted]	[redacted]
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SRF	Sub retinal fluid
TFLs	Tables, Figures, Listings
VA	Visual acuity
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

1 Introduction

This SAP module describes the planned statistical methods for all safety and efficacy analyses. Any changes made to the statistical plan and methodology after the clinical database lock will be documented as an addendum.

The main purpose of this document is to provide summary of the statistical methodology that will be used for this clinical study; this includes a detailed description of data summaries. Analyses plan in this document refers to the related statistical analysis sections in clinical study report.

Data will be analyzed by Novartis according to the data analysis section 9 of the clinical study protocol. That statistical methodology is described below and any deviations from the protocol are documented. Additional detailed information regarding the analysis methodology is contained in the Appendix section.

This SAP describes the planned statistical methods. It is structured as

- A draft of the Clinical Study Report (CSR) Section 16.1.1 (statistical methods planned in the protocol and determination of sample size) and
- A draft of CSR Appendix 16.1.9 (documentation of statistical methods). Appendix 16.1.9 text will contain details of statistical methods and issues that are too long to include in the CSR text.

Please refer to the following document:

- Clinical Protocol CRFB002EJP09

1.1 Study design

This is a 12 month, Phase IV, randomized, open-label, active-controlled, 2-arm, multicenter study. Patients will be randomized in a 1:1 ratio to 1 of the 2 treatment arms:

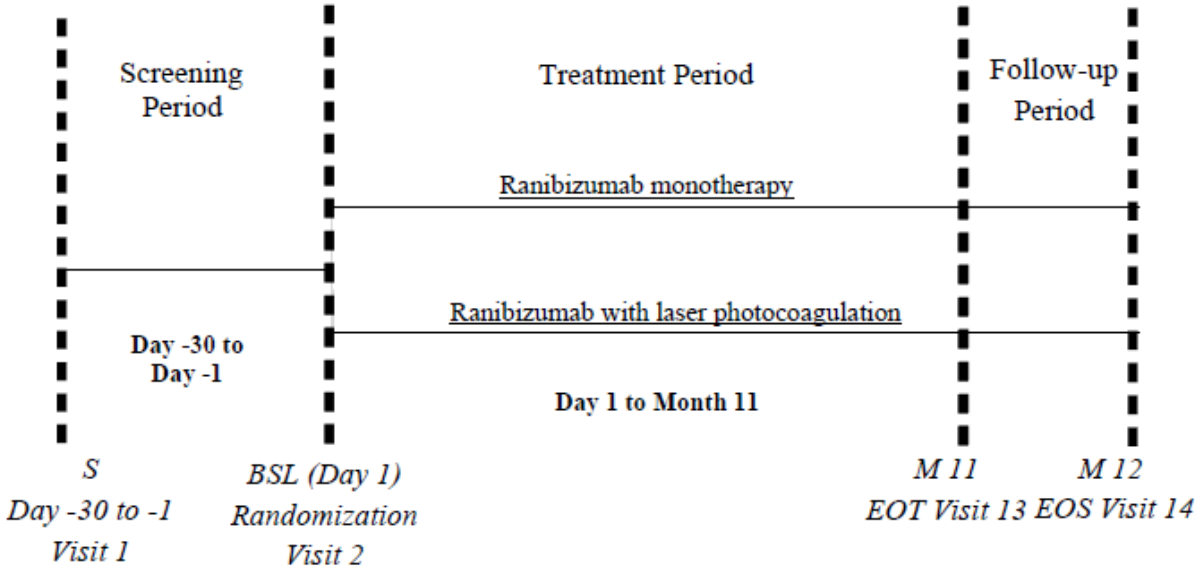
Arm 1: Ranibizumab monotherapy and Arm 2: Ranibizumab with Grid&Direct short pulse laser photocoagulation combination therapy.

In addition to screening and Baseline (Day 1), there will be monthly visits from Month 1 to Month 12.

There will be 3 periods in this study: the Screening Period, Treatment Period and Follow-up Period.

The study design is given in Figure 1-1.

Figure 1-1 Study design



Abbreviations: BSL= Baseline, EOT = End of Treatment Period, EOS = End of Study, S= Screening.

Planned number of patients and randomization

At Baseline (Day 1) at least 56 patients will be randomized. Approximately 70 patients will need to be screened in order to have at least 56 patients eligible and commencing treatment in the trial. Randomization will occur to one of the following two treatment arms in a ratio of 1:1.

Arm 1 (ranibizumab monotherapy)

Patients will start study treatment on Baseline (Day 1) and receive further ranibizumab treatment using PRN regimen i.e., according to the Japanese label of ranibizumab.

Arm 2: (ranibizumab + Grid&Direct short pulse laser photocoagulation combination therapy)

Patients will start study treatment on Baseline (Day 1) and receive further ranibizumab treatment using PRN regimen i.e., according to the Japanese label of ranibizumab. The laser treatment must be given to the target within vascular arcades as soon as indicated.

The criteria for PRN of injections of ranibizumab are described in (protocol Section 5.5.4.2. Refer to (protocol Section 5.5.4) and (protocol Section 5.5.4.1) for more details on treatment administration.

This is an open-label study; therefore treatment blinding (masking) is not applicable. However, masking of the Vision Examiner, assessing parameters constituting the secondary endpoint (BCVA), will be chosen at each site before the study start. Therefore, the Vision Examiner will

not be allowed to access unmasked medical records and to perform any other tasks involving direct patient care which may unmask him/her to the patient's treatment.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients/subjects and investigator staff. A patient randomization list will be produced by the NIRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

The randomization will be balanced by VA (0.3<, or ≥0.3 assessed by decimal VA which is translated into 58 letters in EDTRS or 0.52 in logMAR).

Primary analysis timepoint

The primary analysis will be performed at month 12.

Interim analyses

There are no planned interim analyses.

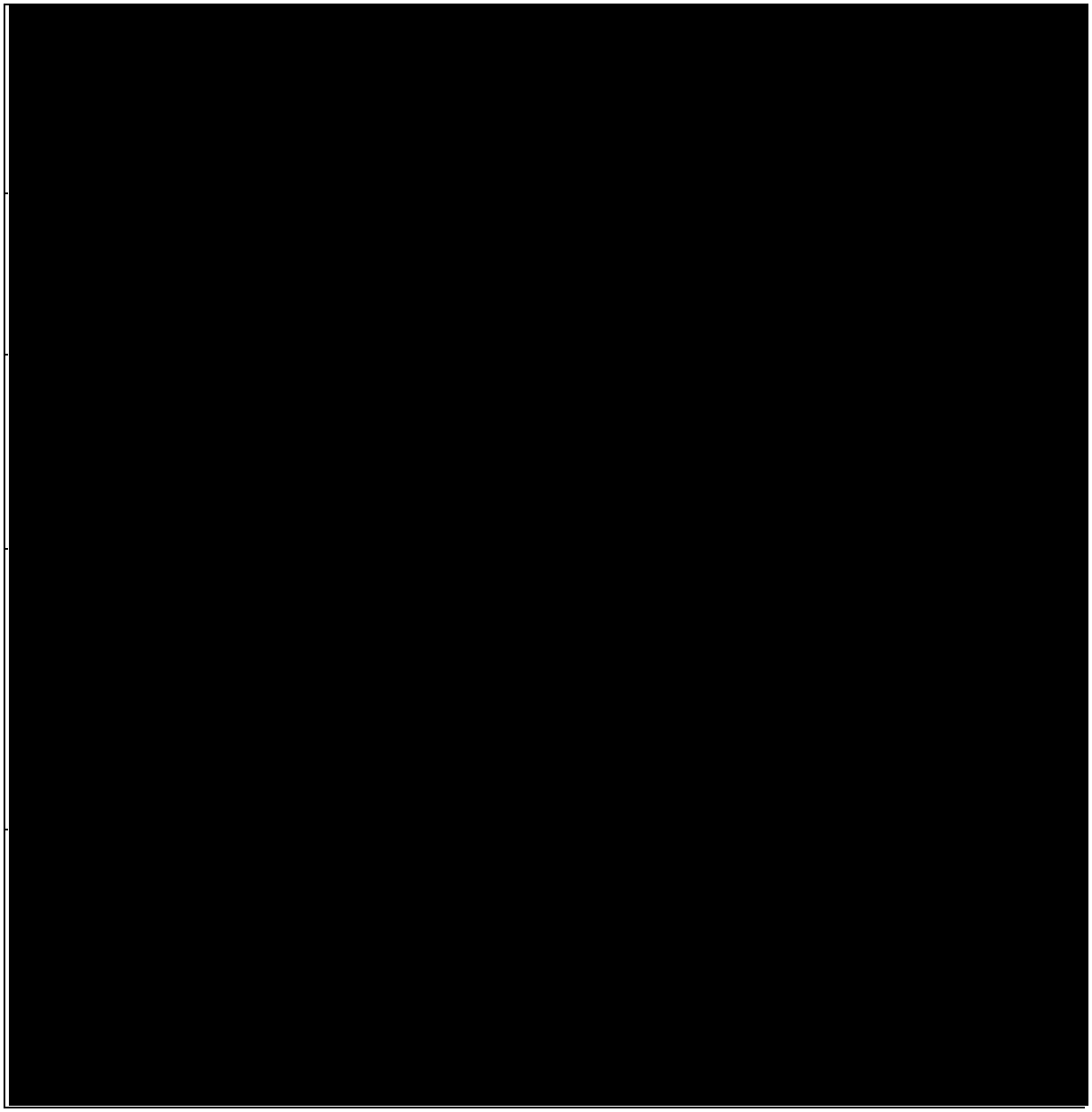
1.2 Study objectives and endpoints

The following objective will be assesed on the patient having ME secondary to BRVO.

Table 1-1 Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
To demonstrate that PRN regimen (PRN, according to the Japanese label of ranibizumab) with 0.5 mg ranibizumab combined with Grid&Direct short pulse laser photocoagulation reduces the burden of frequent ranibizumab injections as compared to ranibizumab monotherapy as assessed by the difference in the mean number of ranibizumab injections applied up to Month 11 between the 2 treatment arms.	The mean number of ranibizumab injections applied up to Month 11 between the 2 treatment arms in patients with visual impairment due to ME secondary to BRVO.
Secondary Objective	
To evaluate the efficacy of each arm as assessed by BCVA and CSFT	The mean change in BCVA from Month 1 through Month 12 compared to Baseline (Day1) using decimal chart converted to be logMAR units, and ETDRS (Month 6, and Month 12) by both the treatment arms. The mean average change in BCVA from Month 1 through Month 12 compared to Baseline (Day1) using decimal chart

	converted to be logMAR units by both the treatment arms. The proportion of patients achieving BCVA improvement of ≥5, ≥10, ≥15, and ≥30 letters and proportion of patients experiencing a loss of <15 letters from Baseline (Day1) to Month 12 by treatment arms. The proportion of patients reaching BCVA values ≥73, ≥80, and ≥85 letters (approximate 0.56, 0.8, and 1.0 Decimal equivalent) at Month 12 by treatment arms. The mean change in CSFT from Month 1 through Month12 compared to Baseline (Day1) by the treatment arms. The mean average change in CSFT from Month 1 through Month12 compared to Baseline (Day1) by the treatment arms.
To evaluate the safety of ranibizumab monotherapy and ranibizumab combined with Grid&Direct short pulse laser photocoagulation therapy in Japanese patients as assessed by the type, frequency, and severity of ocular and non-ocular AEs from Baseline (Day 1) to Month 12.	Overall safety, as measured by type, frequency and severity of ocular and non-ocular adverse events from Baseline (Day 1) to Month 12.
[redacted]	



2 Statistical methods

2.1 Data analysis general information

The analysis will be conducted by Novartis on all patients data after database lock for the respective trial periods. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Analysis datasets and statistical outputs will be produced using the most recent SAS® Version 9.4 (SAS Institute Inc., Cary, NC, USA), and stored in Novartis global programming & statistical environment (GPS).

Data analyses will be presented at all time points assessed, by treatment group including graphical presentations, where appropriate. For statistical analysis purpose, baseline values will be considered to be the last available values collected before Day 1. Day 1 will be defined for statistical analysis purpose as the time point of first treatment (associated to baseline visit).

The efficacy analyses of this study will be based on the study eye data only. For patients who receive a prohibited medication for the study indication in the study eye, the efficacy data will be excluded from the efficacy analysis starting with the time point of this first prohibited treatment.

For non-ocular, study eye, and fellow untreated eye summary tables, figures, and listings will be on all patients included in the population under consideration. Summary tables, figures, and listings for the fellow treated eye will include only those patients in the population under consideration who also received at least one ranibizumab treatment in the fellow eye.

Summary statistics for continuous variables will generally include the number of patients (N), minimum, lower quartile, mean, median, upper quartile, and maximum. For categorical or binary variables, the number and percent of patients in each category will be presented.

If not otherwise specified, p-values and confidence intervals will be two-sided. Unless otherwise stated, the level of significance will be set to 5% (two-sided, family-wise type-I-error).

Assessments documented in the Database as occurring in “both eyes” will be summarized and listed for each eye separately. To facilitate derivations and analysis based on eye (study eye, fellow eye – fellow treated and un-treated) database records for “both eyes” will be split to two records containing identical information as the original record with the exception of the site which shall be recoded to “Right” and “Left”, respectively.

For analysis, endpoints and objectives related to the first treatment interruption due to BCVA stabilization will be analyzed using the first treatment interruption due to disease stabilization.

The obtained decimal VA will be captured in the eCRF, and converted into logMAR (logarithmic minimum angle of resolution) units (absolute values) as the best corrected VA (BCVA) in the conversion formula shown below. A mathematical one-to-one correspondence exists between decimal VA measurements and logMAR values. Therefore, conversion between these units does not produce any error, meaning that any other errors except measurement errors included in decimal VA measurements themselves are not caused.

Conversion formula: logMAR visual acuity = $\log_{10}$ (1/decimal visual acuity) = -$\log_{10}$ (decimal visual acuity).

2.1.1 General definitions

Study treatment

The investigational treatment used in this study is 0.5 mg ranibizumab applied PRN as intravitreal injection of 0.05 mL, with or without the laser treatment.

Study treatment start and end date

Study treatment start date is defined as the first date when a non-zero dose of study drug is administered and recorded on the Drug Administration Record (DAR) CRF page. Similarly, study drug end date is defined as the last date when a non-zero dose of study drug is administered and recorded on the DAR CRF page of the core study.

Study day

Study day will be calculated relative to the date of first study treatment in the study eye (i.e. Day 1). The date of first treatment will be referred to as the "first treatment" date hereafter. For events or assessments which occur on or after the date of first treatment in the study eye, study day will be calculated as event or assessment date – date of first treatment in the study eye + 1. For events or assessments which occur before the date of first treatment in the study eye, study day will be calculated as event or assessment date – date of first treatment in the study eye.

Protocol entry criteria do not require that all patients be eligible for laser application either at time of study entry or randomization. Under the standard of care for laser treatment, if a patient presents with a dense macular hemorrhage and/or severe edema, laser application is to be delayed.

Due to the study drug dosing schedule, one month will be considered as 30 days. However, for "time since event" data (e.g., medical history), one month will be considered as 365.25/12 days for events that occurred prior to study Day 1. Time from events prior to the start of study drug, e.g., time since diagnosis, is calculated as the difference between the start date of study drug and the date of prior event.

Note that, the first dose day is Day 1, and the day before the first dose day is counted as Day -1 (not Day 0).

Study observation periods

In addition to the selection of data based on the the dates of first treatment or treatment decision in the study eye and first ranibizumab treatment in the fellow eye will be used to define the study observation period for each anatomical site (non-ocular, study eye, fellow eye – treated and non-treated) and analysis period. Post baseline assessments will be included in an analysis for a given anatomical site only if the assessment falls in the study observation period for that site for the given analysis period).

Baseline and post baseline

For the study eye, fellow non-treated eye, and non-ocular variables, baseline values will be considered to be the last available non-missing values collected before Day 1. Day 1 will be defined for statistical analysis purpose as the time point of first treatment (associated to baseline visit). (Note, baseline values may include assessments made on a visit day prior to the date of first treatment or pre-treatment assessments made on the date of first treatment.) Post-baseline will always refer to assessments performed after the start of treatment, i.e. after the first study treatment or decision not to treat in the study eye. For the fellow treated eye safety summaries (e.g., intraocular pressure), baseline will be defined similarly using the date of first injection of

ranibizumab in the fellow eye which may be a date after Day 1 (e.g., if the first injection of ranibizumab in the fellow eye is at Month 3, the baseline for the fellow treated eye will be the last assessment prior to the Month 3 visit.) Please see Appendix 16.1.9 in CSR for additional details regarding the definition of baseline for assessments performed on Day 1.

Treatment Period

There is only one treatment period for this study defined as :

From Baseline (Day 1) to Month 11, PRN treatment with monthly monitoring.

Lost to follow up

The patients whose study completion status is unclear because they fail to appear for study visits without stating an intention to withdraw.

On-treatment period

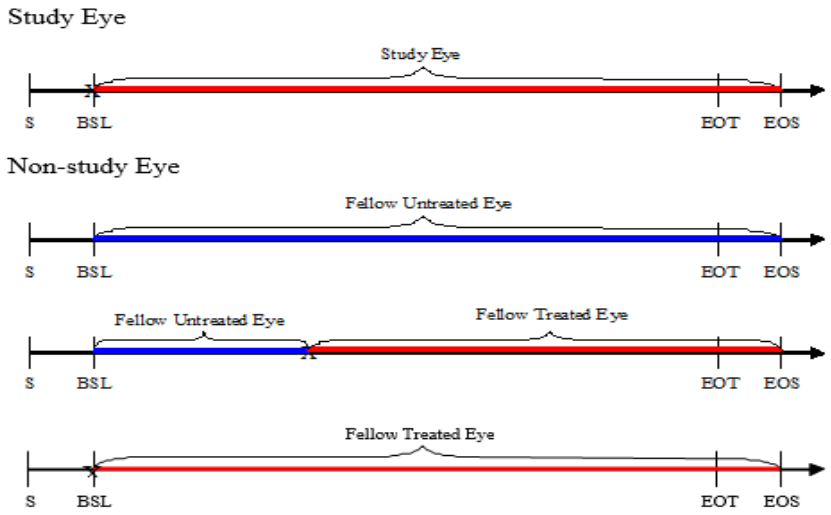
The period where the patients are exposed to the study treatment.

General consideration about Study eye and Fellow eye

The study eye is the eye entered into the database by the investigator to be treated at baseline. The fellow eye will be defined as the fellow untreated eye if the fellow eye has not been treated with ranibizumab. The fellow eye is the fellow untreated eye until treated with ranibizumab and then becomes the fellow treated eye in Figure 2-1.

Note: Not all fellow eyes will be treated with ranibizumab and a fellow eye may be a fellow untreated eye for the entire study duration. Alternatively, the fellow eye may be treated at baseline and will be the fellow treated eye throughout the study duration.

Figure 2-1 Study Eye, Fellow Untreated Eye and Fellow Treated Eye



S=Screening, BSL=Baseline, EOT=End of Treatment, EOS=End of Study, X=First treatment decision for study eye, X=First ranibizumab treatment in the non-study eye

2.2 Analysis sets

The following analyses sets will be used in this trial:

The **Screened Set** will consist of all screened patients.

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

The Full Analysis Set (FAS) will consist of all randomized patients who received at least one administration of ranibizumab injection. In case there are safety concerns after administration of laser photocoagulation at Baseline (Day 1) and ranibizumab injection is not given during the entire study, the patient will still be included in the FAS, as there was an intention to treat the patient with ranibizumab. Following the intent-to-treat principle, patients will be evaluated according to the treatment assigned to at randomization.

No data will be excluded from the FAS analyses because of protocol deviations.

The Per Protocol Set (PPS) will consist of all patients in the FAS who received at-least the first mandatory administration of ranibizumab injection and have at least one post-baseline assessment for BCVA and have no clinically significant protocol deviations.

Clinically significant protocol deviations will be defined in the Statistical Analysis Plan. The criteria and determination of clinically relevant protocol deviations and patient specific identification of data to be excluded from the PPS will be databased and finalized prior to database lock.

The **Safety Set** will consist of all patients who received at least one administration of ranibizumab injection and had at least one post-baseline safety assessment. The statement that a patient had no AEs also constitutes a safety assessment. Patients will be evaluated according to treatment received.

2.3 Patient disposition, demographics and other baseline characteristics

Summary statistics will be presented for continuous, demographic and baseline characteristic variables (including the baseline values of the secondary efficacy variables) for each treatment group and for all patients in the randomized set. The number and percentage of patients in each category will be presented for categorical variables for each treatment group and all patients.

Demographic and baseline disease characteristics will be summarized for the variables listed in Section 2.3.2.

2.3.1 Patient disposition

Disposition (study completion) at Month 12 will be summarized by tabulating the number and percentage of patients that completed the trial period and also those that discontinued in that trial period, with discontinuations categorized by reason.

Treatment completion will be summarized in the same manner as patient disposition using data from the treatment completion eCRF page. The last dose date for the treatment will be used as the date of treatment completion or early termination of treatment as dosing is PRN and the date of last treatment recorded on the treatment completion page is the date of last treatment actually

given, not the date of the last treatment decision (including decisions not to treat). Disposition and treatment completion will be summarized for patients in the Randomized Set for the Month 12 analysis. Disposition and treatment completion will also be summarized by the visit of termination/completion. Disposition and treatment completion data will also be presented in listings.

The total number of patients screened, randomized and the number of patients screened, but not randomized will be summarized, including the reason for screening failure. Demographic data and the reason for non-inclusion into the study will be listed for patients who fail screening. Screening failure summaries will be performed for the Month 12 analysis.

All protocol deviations will be summarized through presenting the 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 for the Month 12 analysis.

2.3.2 Patient demographics and baseline characteristics

Descriptive statistics will be provided for patient demographics and baseline ocular characteristics (identification of study and fellow eye (right/left), type of retinal vein occlusion, intraocular pressure (IOP), [redacted] Color Fundus Photography (CF) and [redacted] including the baseline values of the primary and secondary efficacy variables (best-corrected visual acuity (BCVA) by decimal VA test and ETDRS charts, central subfield thickness (CSFT)) will be summarized for the Randomized Set for the Month 12 analysis.

Eye specific assessments will be summarized separately for study eye and fellow eye with the exception of [redacted] CF, [redacted] which will be summarized for study eye only. [redacted]

The following demographics data will be analyzed as described below:

Continuous variables:

- Age (years), Height (cm), Weight (kg), BMI.

Categorical variables:

- Age group (<65, ≥ 65 years)
- Gender (male, female)
- If female then child bearing potential (Able to bear children, Premenache, Post menopausal, Surgically sterile)
- Race (Asian, Other)
- Ethnicity (Japanese, Other).

The following vital signs data will be analyzed as described below:

Continuous variables:

- Sitting pulse rating (bpm), sitting diastolic blood pressure (mmHg), and sitting systolic blood pressure (mmHg)

Categorical variables:

- Smoking History (Current, Former, Never)
- Coexistence of hypertension (Yes/No)
- Coexistence of Diabetes (Yes/ No)
- Coexistence of Hyperlipidemia (Yes/ No)

The following baseline characteristics data will be analyzed as described below:

Continuous variables:

- Decimal BCVA (converted to logMAR)
- ETDRS BCVA (letters)
- CSFT (μm)
- Intraocular pressure (mmHg)
- Time since first symptom of BRVO (month)

Categorical variables:

- Study Eye (left, right)
- Presence of RVO (Yes, No)
- Presence of macular edema (Yes. No)
- Presence of other things (Yes, No)
  - Time since first symptom of BRVO (< 3 months, => 3 months to < 6 months, >= 6 months)
- ETDRS BCVA (letters) (≤39, 40-59, ≥60)
- Decimal BCVA (<0.3, or ≥0.3) (equivalent to 0.52 in logMAR)
- Prior RVO treatment (Yes, No)
  - Type of prior RVO treatment (anti-VEGF agent, Steroids, Ocular circulation ameliorator, Anticoagulant drug, Prostaglandin, Focal/grid laser, Sector/pan-retinal laser, Vitrectomy, Other)
  - Site (Non-ocular, Study eye, Fellow eye, Both eye)

Baseline assessed [redacted]/Color fundus photography(CF)

Categorical variables:

- Presence of macular edema (Yes, No, Not evaluable) (as detected [redacted] within ETDRS grid)
- Presence of capillary leakage (Yes, No, Not evaluable)

[redacted]

[redacted]

2.3.3 Medical History/ current medical condition

Relevant medical history (ocular and non-ocular) and current medical conditions will be tabulated by site (non-ocular, ocular (study/fellow eye)), system organ class (SOC) and preferred term of the MedDRA dictionary. Other relevant baseline information will be listed and summarized as appropriate with descriptive statistics. Analyses will be based on the Randomized Set.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

2.4.1.1 Study treatment

The number of eyes treated with ranibizumab will be summarized by the number and percentage of patients receiving treatment in one or both eyes using Safety Set.

Additionally the number and percentage of patients with simultaneous bilateral treatment with ranibizumab will be presented. A patient will be considered to have simultaneous bilateral treatment with ranibizumab if the patient received 3 or more injections of study drug (study and fellow treated eye) within a 37-day period (i.e., date of the third injection in the series – date of first injection in the series < 37.)

The number and percentage of patients receiving at least one laser application in the study eye will also be summarized.

The duration of the study observation period will be summarized descriptively for the study eye, the fellow untreated eye, and the fellow treated eye. Durations will be calculated as period end date – period start date + 1 for the study eye, fellow untreated eye. For fellow eyes that do receive an injection of study drug prior to the data cut off, the duration for the fellow untreated eye will be calculated as period end date – period start date.

The number of injections administered per patient for injections in the study eye, injections in the fellow treated eye, and for injections in either eye at each visit will be summarized. Additionally, the reasons of retreatment criteria (when ranibizumab will be given in PRN period) and when ranibizumab will not be given (as per protocol, stabilization criteria) and will be given (retreatment criteria) will be summarized by visit and eye (study eye and fellow treated eye). The denominator at each visit will be the number of patients who for which a treatment decision was recorded in the eCRF for the given eye at that visit. If a patient receives more than one injection during a given visit window, the patient will be counted only once in the number receiving an injection and only once the denominator; however the reason for dosing for both doses will be tabulated. The number and percentage of patients receiving a laser application in the study eye at each visit and the reasons for treatment given or not given will be summarized in similar manner as injections.

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/eye will be presented. The number of laser applications per patient in the study eye will also be summarized by type (grid, direct, both), frequency distribution and summary statistics in similar manner to injections. Multiple sessions for the initial laser treatment will be counted as 1 application for analysis. Additionally the summary of laser treatment will also be performed separately for initial and subsequent laser administrations. Additionally, injection summaries for the study eye up to Month 11 will be presented for each subgroup as listed in the efficacy subgroup analyses section.

Injections and laser applications given at unscheduled visits will be mapped to study visits as per the visit windows.

The pattern of ranibizumab treatment administrations will be summarized for the study eye. For a given patient, the pattern of ranibizumab treatments will be identified by a series of zero's, one's (and possibly two's) and the letters or D, where a zero indicates the visit occurred and no injection given, and a one (or two) indicates an injection was given, a D indicates the patient discontinued the study prior to that visit. In the event that a patient receives two injections within a given visit window, a 2 will be displayed at that visit in the pattern of ranibizumab treatment administration. The number and percentage of patients for each observed dosing pattern will be presented. The pattern of laser administrations will be summarized in a similar manner for the study eye for patients randomized to the ranibizumab with Grid&Direct short pulse laser photocoagulation arm. Initial laser treatments consisting of multiple sessions will be included within the pattern once, for the visit at which the first session was administered. Additionally the pattern of laser treatment will also be performed by considering initial and subsequent laser administrations separately.

For the study eye, the first visit where an injection was not given due to disease stabilization will be summarized by the number and percentage of patients whose first treatment interruption due to disease stabilization occurred at a given visit. This summary will include both patients randomized to the ranibizumab monotherapy and ranibizumab with Grid&Direct short pulse laser photocoagulation arm.

The ranibizumab dosing administration record will be listed for all patients with a separate listing for the set of patients who received simultaneous bilateral treatment with ranibizumab. The laser application record will be listed for all patients. Additionally, a listing of summarized dosing parameters (e.g., total number of injections and laser applications in the study eye) will be provided. A listing will also be provided detailing data related to the study observation period.

Patients receieving laser exposure <0.02 and >0.03 will be flagged as low and high respectively in the listing.

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after enrolling into the study will be summarized by preferred term and ATC class of the World Health Organization (WHO) Drug Reference List.

Concomitant or prior medications entered into the database will be coded using the WHO Drug Reference List. Medical history/ current medical conditions and AEs will be coded using MedDRA terminology.

2.4.2.1 Prior and concomitant therapies

Summaries will be presented for time periods: therapies received prior to the start of study treatment (i.e. medication end date is prior to date first treatment in the study eye) and therapies received after the start of study treatment. For prior medications, separate summaries will be provided for non-ocular, study eye, and fellow eye. For concomitant medications, separate summaries will be provided for non-ocular, study eye, untreated fellow eye, and fellow treated 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. If the site is missing, the data will be queried. However, if this issue is not resolved in the data, then each case will be reviewed by the Clinical team (prior to the database lock) and a decision will be made to determine if the medication is non-ocular or ocular. If the medication is ocular, then the medication will be allocated to both study eye and fellow eye. This medical review process will be performed outside of the database and will be implemented programmatically in the analysis data sets.

Concomitant medications will be summarized for the Day 1 to Month 12 analysis periods.

2.4.2.2 Prohibited medication

The ocular treatments which are not allowed in the study eye/ both eyes or systemic medications which are not allowed throughout the entire study, will be summarized similary to concomitant medications.

2.5 Analysis of the primary objective

The primary objective is to demonstrate that PRN regimen of 0.5 mg ranibizumab with Grid&Direct short pulse laser photocoagulation reduces the burden of frequent ranibizumab injections as compared to ranibizumab monotherapy.

2.5.1 Primary endpoint

The primary endpoint is the difference in the mean number of ranibizumab injections applied up to Month 11 between the 2 treatment arms in patients with visual impairment due to ME secondary to BRVO.

The primary analysis will be conducted at Month 12 within the FAS set using observed data.

2.5.2 Statistical hypothesis, model, and method of analyses

The null hypothesis to be rejected is that the mean values of the the number of injection for both treatments arms are same. The corresponding alternative hypothesis is that the mean values of number of injections of Ranibizumab with laser therapy is less than the mean values of the number of injections of the Ranibizumab monotherapy.

The following 1-sided hypothesis will be tested at the alpha level of 0.025:

H_0: $\mu_{\text{Ranibizumab-Laser}} - \mu_{\text{Ranibizumab-Mono}} = 0$ versus

H_1: $\mu_{\text{Ranibizumab-Laser}} - \mu_{\text{Ranibizumab-Mono}} < 0$

where $\mu_{Ranibizumab-Laser}$ and $\mu_{Ranibizumab-Mono}$ are the unknown mean values of the number of ranibizumab injections for the related treatment arms up to Month 11.

The statistical hypothesis testing of the number of ranibizumab treatments will be based on a stratified Cochran-Mantel-Haenszel (CMH) test the observed values as scores and the row mean scores statistic. Stratification will be done based on categories of baseline decimal BCVA (<0.3, or ≥ 0.3, equivalent to 0.52 in logMAR). Difference of mean number of injections, 95% confidence interval (CI) of difference will be done by two sample t-test and one-sided p-value (Score=Table in SAS) of the CMH test will be reported. As the CMH test produces a two-sided p-value, if the direction of the observed difference supports the superiority outcome (e.g. mean difference < 0), the two-sided p-value will be converted to a one-sided p-value by dividing by two. Otherwise, the one-sided p-value will be calculated as 1 - (the two-sided p-value divided by two).

In addition to that, the frequency of patients by number of injections will also be summarized.

2.5.3 Handling of missing values/censoring/discontinuations

No imputation is required for the primary endpoint which is number of ranibizumab injections, based on PRN regimen that is the number of injections during the study period will be used for the primary endpoint.

2.5.4 Supportive analyses

For sensitivity purposes, the primary analysis will be repeated for the PPS. Any major discrepancies in the results across analyses will be investigated as necessary.

The primary analysis will also be supported by doing a stratified non-parametric Wilcoxon-Mann-Whitney test. Which is equivalent to the CMH test using non-paramtric approach (Score=Rank) option in SAS.

Additionally, to evaluate the difference in number of injections, the primary analysis will also be based only on patients who completed the study.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

Refer to Table 1-1 of section 1.2 for the list of secondary objective. All of the endpoints will be summarized descriptively. Summary statistics will include number of patients (N), minimum, lower quartile, mean, median, upper quartile and maximum and will also be provided in data listings.

2.7.1 Secondary endpoints

The secondary analysis will be conducted within the FAS using the LOCF approach and observed data.

Refer to Table 1-1 of section 1.2 for the list of secondary endpoints.

2.7.2 Statistical hypothesis, model, and method of analysis

BCVA (Decimal and ETDRS) from Month1 through Month 12

Loss / Gain of Visual Acuity (VA) based on BCVA Decimal

If change (Postbaseline upto Month 12 - Baseline) of BCVA decimal value from baseline is < 0, it is considered as loss of BCVA and indicates lost in visual acuity.

Where as, If change of BCVA decimal value from baseline is >0, it is considered as gain of BCVA and indicates gained in visual acuity.

Loss / Gain of Visual Acuity (VA) based on BCVA LogMAR

If change (Postbaseline upto Month 12- Baseline) of LogMAR value from baseline is < 0, it is considered as loss of LogMAR and indicates gained in visual acuity.

Where as, If change of LogMAR value from baseline is > 0, it is considered as gain of LogMAR and indicates lost in visual acuity.

Loss / Gain of Visual Acuity (VA) based on BCVA ETDRS Letters

If change (Postbaseline upto Month 12- Baseline) of ETDRS Letters from baseline is < 0, it is considered as loss of BCVA letters and indicates lost in visual acuity.

Where as, change (Postbaseline upto Month 12- Baseline) of ETDRS Letters from baseline is > 0, it is considered as gain of BCVA letters and indicates gained in visual acuity.

Mean Change

To obtain the mean change in BCVA at Month x the sum of single patient's change in BCVA at month x from baseline will be divided by the number of patients.

The mean change in BCVA at Month 6 and Month 12 will be compared to Baseline (Day1) using decimal chart (converted to logMAR) and ETDRS (at Month 6, and Month 12) between the 2 treatment arms. The analyses at each visit will be based on an analysis of variance (ANOVA) model with treatment group, and stratification factors. Stratification will be done based on categories of baseline decimal BCVA (<0.3, or ≥0.3, which is translated to 58 letters in ETDRS or 0.52 in logMAR).

The Least Squares Means (LS Means) estimates of BCVA compared to Baseline (Day1), difference of LS Means, their 95% confidence interval (CI) and the p-value (related to the null hypothesis that difference in mean change is zero) will be reported. To incorporate the imbalance (if any) the ObsMargin (OM) option may be used in determining the least squared means.

Additionally, by visit ANOVA models will also be perfomed for all the months for decimal BCVA (converted to logMAR) including visit as a model factor. The LS means (bar graphs for ETDRS) will also be presented graphically using change from baseline and absolute values plots for all months separately for decimal and ETDRS BCVAs.

Mean Average Change

The mean average change in BCVA from Month 1 through Month 12 will be compared to baseline using for decimal chart converted to be logMAR units by both the treatment arms.

To obtain the mean average BCVA change from Month 1 through Month 12, the sum of single patient's average BCVA changes will be divided by the number of months.

The average change in BCVA will be calculated for each single patient as follows:

$$\text{Average } \Delta \text{ BCVA} = \frac{\Delta \text{ BCVA}_{M1} + \Delta \text{ BCVA}_{M2} + \ldots + \Delta \text{ BCVA}_{M12}}{12}$$

where BCVA_{Mx} = change in BCVA from Baseline (Day1) at Month x.

The analyses at each visit will be based on an analysis of variance (ANOVA) model with treatment group, and stratification factors. Stratification will be done based on categories of baseline decimal BCVA (<0.3, or ≥0.3, which is translated to 0.52 in logMAR).

The Least Squares Means (LS Means) estimates of BCVA compared to Baseline (Day1), difference of LS Means, their 95% confidence interval (CI) and the p-value (related to the null hypothesis that difference in mean change is zero) will be reported. To incorporate the imbalance (if any) the ObsMargin (OM) option may be used in determining the least squared means.

Categorized Change

Endpoints for BCVA improvement of ≥1, ≥5, ≥10, ≥15, and ≥30, BCVA attainment of ≥ 73, ≥ 80 and ≥ 85 letters and BCVA improvement of ≤ -0.02, ≤ -0.1, ≤ -0.2, ≤ -0.3, and ≤ -0.4 LogMAR, BCVA attainment of ≤ 0.24, ≤ 0.1 and ≤ 0.0 LogMAR or BCVA loss <15 letters and BCVA loss ≤ 0.3 LogMAR will be summarized by presenting the number and percentage of patients in each treatment achieving the endpoint and the corresponding 95% confidence intervals based on exact methods. Treatment differences for the percentages will also be presented along with their 95% confidence intervals based on normal approximation for differences in percentages. P-values for the differences will also be presented based on the Cochran-Mantel-Haenszel general association test with stratification based on baseline BCVA (baseline BCVA <0.3, or ≥0.3, which is translated to 58 letters in ETDRS or 0.52 in logMAR).

Note: a loss of < 15 letters includes patients who have gained visual acuity.

The number and proportion of patients reaching BCVA values ≥73, ≥80, and ≥85 letters and BCVA ≤ 0.24, ≤ 0.1 and ≤ 0.0 LogMAR(approximate 0.56, 0.8, and 1.0 Decimal equivalent) at Month 12 will also be summarized by treatment arms and for all visits.

BCVA will be presented in data listings.

CSFT from Month 1 through Month 12

Mean Change

To obtain the mean change in CSFT at Month x the sum of single patient's change in BCVA at month x from baseline will be divided by the number of patients.

The mean change in CSFT at Month 6 and Month 12 will be compared to Baseline (Day1) between the 2 treatment arms. The analyses at each visit will be based on an analysis of variance (ANOVA) model with treatment group, and stratification factors. Stratification will be done based on categories of baseline CSFT (<450 μm,and >= 450 μm) and OCT machine type.

The Least Squares Means (LS Means) estimates of CSFT compared to Baseline (Day1), difference of LS Means, their 95% confidence interval (CI) and the p-value (related to the null hypothesis that difference in mean change is zero) will be reported. To incorporate the imbalance (if any) the ObsMargin (OM) option may be used in determining the least squared means.

Additionally, by visit ANOVA models will also be perfomed for all the months of CSFT including visit as a model factor. The LS means will also be presented graphically using change from baseline and absolute values plots for all months.

Mean Average Change

The endpoints related to CSFT parameter can be calcualted and analyzes in following way.

The mean average change in CSFT from Month 1 through Month 12 will be compared to baseline by both the treatment arms.

To obtain the mean average CSFT change from Month 1 through Month 12, the sum of single patient's average CSFT changes will be divided by the number of patients.

The average change in CSFT will be calculated for each single patient as follows:

$$\text{Average } \Delta \text{ CSFT} = \frac{\Delta CSFT_{M1} + \Delta CSFT_{M2} + \cdots\cdots\cdots\cdots\cdots + \Delta CSFT_{M12}}{12}$$

where $CSFT_{Mx}$ = change in CSFT from Baseline (Day1) at Month x.

The analyses at each visit will be based on an analysis of variance (ANOVA) model with treatment group, and stratification factors. Stratification will be done based on categories of baseline CSFT (<450 μm, and ≥ 450 μm) and OCT machine type.

The Least Squares Means (LS Means) estimates of CSFT compared to Baseline (Day1), difference of LS Means, their 95% confidence interval (CI) and the p-value (related to the null hypothesis that difference in mean change is zero) will be reported. To incorporate the imbalance (if any) the ObsMargin (OM) option may be used in determining the least squared means.

Additionally, by visit ANOVA models will also be perfomed for all the months including visit as a model factor. The LS means will also be presented graphically using change from baseline and absolute values plots for all months.

2.7.3 Handling of missing values/censoring/discontinuations

For the secondary efficacy variables (BCVA, CSFT etc.), the analysis will follow a LOCF approach with the specification that missing values will be replaced by the last post baseline observation before the missing time point.

2.7.4 Supportive Analyses

For sensitivity purposes, the secondary efficacy analysis will be repeated for the PPS population using as observed and LOCF approach. Any major discrepancies in the results across analyses will be investigated as necessary.

2.7.5 Subgroup Analyses

Summary statistics will be presented for the BCVA mean change from baseline by visit for the subgroups identified below at the 12 Month analyses for the FAS using LOCF. Figures will also be produced to show the BCVA mean change from baseline by visit over time by treatment and subgroup. The primary endpoint, i.e., the number of treatments will also be summarized based on these subgroups. Since the sample size is less, some of the subgroup levels may have very less counts, so summarizing may not be meaningful. If the number of patients at each level of a subgroup are less than 5 then summry will not be created for that level.

[redacted]

- Baseline ETDRS BCVA (<58 letters and >= 58 letters)
- Decimal BCVA (<0.3, or ≥0.3) (equivalent to 0.52 in logMAR)

[redacted]

2.8 Safety analyses

All safety analyses will be performed using observed data in the Safety Set using observations as specified for the non-ocular, study eye, fellow eye – treated and un-treated. Summaries will be done for each treatment group as well as Total arm column.

2.8.1 Adverse events (AEs)

Adverse events will be deemed treatment emergent if the onset date is on or after start of study treatment /Day 1. All treatment-emergent AEs will be summarized. Any AEs recorded prior to the start of study treatment/Day 1 will be listed separately and together with all other AEs. If any event has an incomplete onset date, this will be handled as described in the missing or incomplete data imputation section in the Appendix.

Adverse events will be presented separately by site (non-ocular, study eye, fellow eye – treated and un-treated) based on the site information as recorded in the database. Adverse events that are reported for both eyes will be summarized and listed for the study eye and the fellow eye (fellow untreated and fellow treated as applicable.) Adverse events will be summarized by presenting the number and percentage of patients having an AE in each primary system organ class and having each individual AE based on the preferred term. Patients who experienced

multiple AEs for a preferred term will be counted once, similarly for patients with multiple AEs per system organ class.

The following AE summaries will be presented for non-ocular events, study eye events, fellow eye events – treated and un-treated events for Day 1 to Month 12.

- all adverse events,
- adverse events by maximum severity,
- serious adverse events,
- adverse events leading to study treatment discontinuation,
- adverse events leading to dose adjustment or study treatment interruption,
- adverse events suspected to be related to study drug,
- adverse events suspected to be related to ocular injection, and
- adverse events suspected to be related to study drug and/or ocular injection.

Additionally, summaries will be presented for study eye and non-ocular all adverse events and all serious events from the first ranibizumab injection in the study eye to Month 12 for combination theraphy patients. Summaries will also be presented for all study eye, fellow treated eye, and non-ocular adverse events from Day 1 to Month 12 for patients who receive simultaneous bilateral treatment.

The number and proportion of patients who experience at least one event of increased IOP (based on preferred term) will be summarized. The number of occurrences of increased IOP per patient will be summarized by number and percentage of patients with each number of occurrences (1 occurrence, 2 occurrence, etc.). Summary statistics will be presented for the duration of increased IOP events.

[redacted]

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 or laser as applicable) and relative (in number of days) to the Day 1.

The following AE listings will be provided:

- deaths,
- serious adverse events,
- adverse events leading to study treatment discontinuation,
- adverse events leading to study treatment adjustments or interruption,
- any AE recorded prior to the start of study treatment/Day 1,
- any treatment emergent AEs with the exception of ocular AEs of the fellow eye (treated and untreated). Untreated is starting on or after first treatment with ranibizumab within

this eye, and treated is starting on or after the first treatment with ranibizumab within this eye, and

- any AE for patients who received 3 or more injections of study drug with a 37-day period (i.e., adverse events for patients who receive simultaneous bilateral treatment with ranibizumab).
- Adverse events of interest including neovascular complications, events related to BRVO, macular edema, and glaucoma.

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable

2.8.2 Deaths

Separate summaries and listings will be provided for deaths.

2.8.3 Laboratory data

Laboratory data for two groups of tests (hematology and chemical chemistry) will be summarized by presenting shift tables using extended normal ranges with thresholds representing clinical relevant abnormality and by presenting descriptive statistics of raw data and change from Baseline (Day1). Values outside the extended normal range will be listed by patient and treatment arm and flagged in data listings. Below are the ranges which will be used for shift tables.

- Central laboratory assessment: (normality)
  - Leptin (male; normal range <=13.0, or >0.9 ug/L, female; <=21.8, or >2.5 ug/L)
  - Total cholesterol (normal range <=5.663, or >=3.362 mmol/L)
  - LDL cholesterol (normal range <=3.595, or >=1.034 mmol/L)
  - Creatinine (male; normal range <=91.9, or >=53.9 umol/L, female; normal range <=69.8, or >=41.5 umol/L)
  - highly sensitive CRP (<=2.0 mg/L)
  - Hematocrit (male; normal range <=52.4, or >=39.7 %, female; normal range <=45.0, or >=34.8 %)
  - VEGF (normal range <=38.3, ng/L)

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Not applicable.

2.8.4.2 Vital signs

Vital signs will be summarized for all visits by presenting shift tables using thresholds representing clinical relevant abnormality and by presenting descriptive statistics such as mean median, minimum and maximum of raw data and change from Baseline (Day1). Values outside

the extended normal range will be listed by patient and treatment arm and flagged in data listings.

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

Analysis will be based on the patients in the Safety Set for the Day 1 to Month 12 period. Patient listings will be provided and values outside these critical value ranges will be flagged.

Clinically notable abnormal vital signs values for adults

Variable	Criterion Value	Change Relative to Baseline
Heart Rate	≥ 120 b.p.m. ≤ 50 b.p.m.	increase of ≥ 15 b.p.m. decrease of ≥ 15 b.p.m.
Systolic blood pressure	≥ 180 mm Hg ≤ 90 mm Hg	increase of ≥ 20 mm Hg decrease of ≥ 20 mm Hg
Diastolic blood pressure	≥ 105 mm Hg ≤ 50 mm Hg	increase of ≥ 15 mm Hg decrease of ≥ 15 mm Hg

2.8.4.3 Intraocular pressure (IOP)

Intraocular pressure absolute values and changes from Baseline by visit and changes from pre-dose to post-dose assessments within a visit will be descriptively summarized. Additionally, the number and percentage of patients with IOP ≥ 30 mmHg will be presented by visit for pre-injection and post-injection/ laser assessments as well as for any post-baseline IOP (pre-injection or post-injection/ laser), any post baseline pre-injection assessment (not including the assessment prior to first treatment in the study eye), and any post-injection/ laser assessments. Summaries will be presented separately for the study eye and for the fellow treated eye for the Day 1 to Month 12 period. For the fellow treated eye summary, eyes will only be included for visits at or after the first injection of ranibizumab in the fellow eye. Baseline IOP for the fellow treated eye will be the last assessment in the fellow eye prior to the first injection of ranibizumab in that eye.

IOP data will be listed for all patients and for the set of patients who have at least one IOP value ≥ 30 mmHg. Additionally, a listing will be provided for patients who have a post- injection IOP assessment ≥ 25 mmHg followed by a pre-injection IOP assessment ≥ 25 mmHg within the same eye at the next scheduled visit.

2.8.4.4 Prior RVO treatment

This will consist of summerizing the type of prior RVO treatment for different site (Non ocular, Study eye, Fellow eye, Both eye). Summaries will include the number and proportion of patients.

Antibiotic medications will also be listed.

2.8.4.5 Ophthalmic examination and post injection/ laser assessments

Ophthalmic examination and post-injection/ laser safety assessments (not including IOP, CF [redacted]) results will only be listed. All Post laser assessments of CF [redacted] parameters will be summarized separately.

2.8.4.6 Pregnancy

Child bearing potential and serum and urine pregnancy test results (if applicable) will be listed for female patients.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

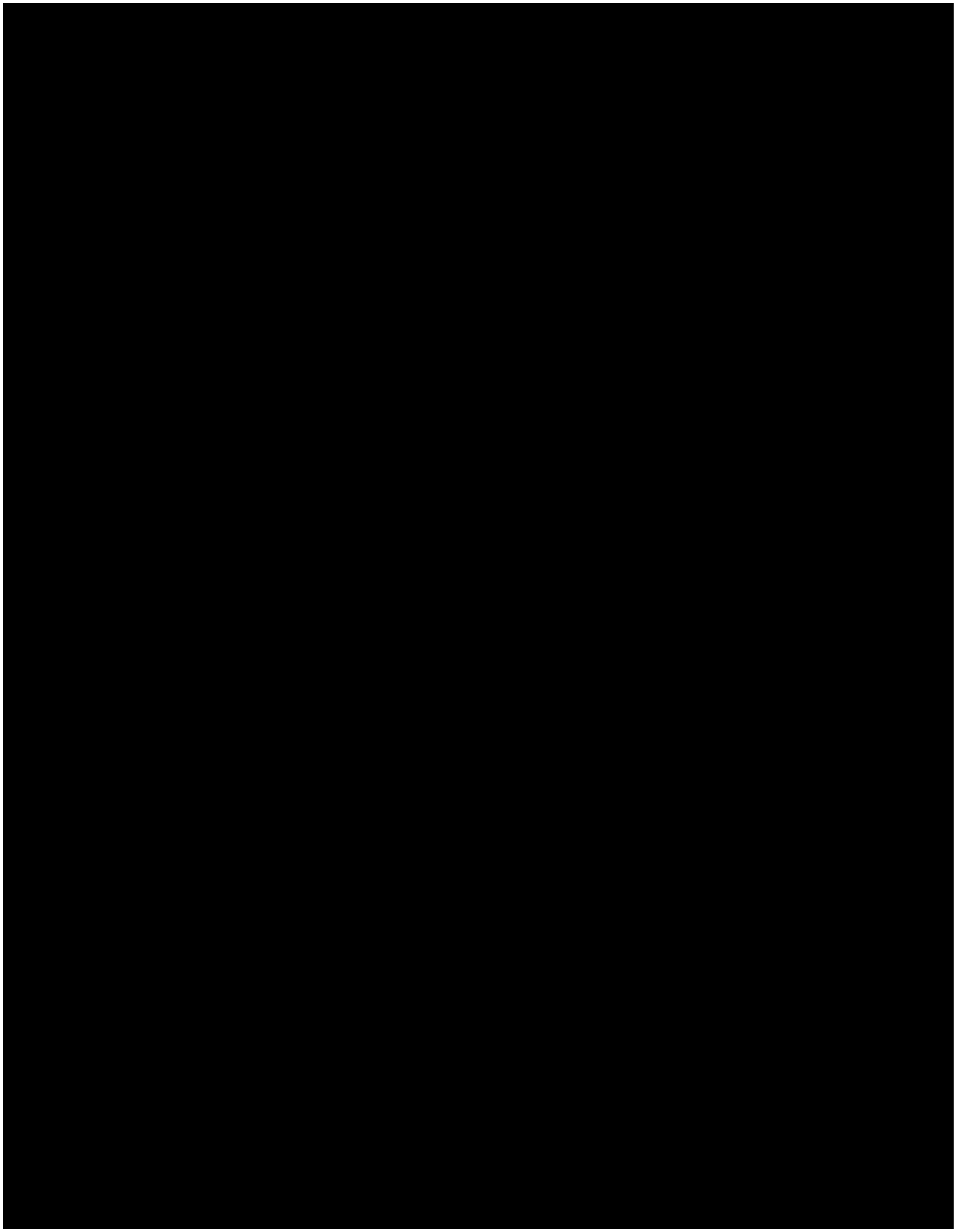
2.11 Patient-reported outcomes

Not applicable.

2.12 Biomarkers

Not applicable.

[redacted]



2.14 Methodology

2.14.1 Predictors of outcomes

In this subsection, analysis will be applied to observed case and repeated for Last Observation Carried Forward (LOCF) where of interest.

The following modelling steps will be used:

1. Test the importance of individual predictor on response variable using linear regression for continuous predictor and one-way analysis of variance (ANOVA) categorical predictor for continuous response (BCVA change, absolute value and number of injection). Logistic regression will be used when response variable is binary. Inclusion in multiple regression model when $p < 0.2$.
2. Repeat Step 1 for each treatment group separately to test for treatment interactions.
3. For each predictor which appeared to be significant in at least one of the treatment groups tested by step 2, introduce the interaction between treatment group and that predictor.
4. Use backward stepwise regression procedure to choose the optimal set of predictors from the set of predictors meeting the required criteria in step 1 and step 3. Significance level to stay in multiple regression model when $p < 0.05$.

   In case of no significant predictors, univariate selection will be repeated when $p < 0.1$ and again verified through the stepwise regression. If no predictors remain again then stop.
5. For multiple linear regression analysis, estimated coefficients along with their 95% confidence intervals (CI) and p-values will be reported. If the model is logistic regression, estimated coefficients along with their 95% CI and p-value, and odds ratios along with their 95% CI will be reported.

2.14.1.1 Model predictors

Table 3-1 List of models

Model type	Response	Population	Possible predictors
Multiple linear regression	BCVA change (letters) from baseline at Month 12	FAS as observed / FAS (LOCF)	Treatment regimen, age, sex, smoking history, BMI, presence of hypertension at baseline, presence of prior RVO treatment, baseline BCVA (letters), baseline BCVA (log MAR), baseline CSFT, presence of SRF at baseline, presence of cysts at baseline, [redacted] Average retinal sensitivity (Total) at baseline, Average retinal sensitivity (Foveal area) at baseline, Average retinal sensitivity (Affected side) at baseline, Average retinal sensitivity (Unaffected side) at baseline, Leptin (male; <=13.0, or >13.0 ng/mL, female; <=21.8, or >21.8 ng/mL) at baseline, Total cholesterol (<=219, or >219 mg/dL) at baseline, LDL cholesterol (<=139, or >139 mg/dL) at baseline, Creatinine (male; <=1.04, or >1.04 ng/dL, female; <=0.79, or >0.79 ng/dL) at baseline, highly sensitive CRP (<0.2, or ≥0.2 mg/dL) at baseline, Hematocrit (male; <=52.4, or >52.4 ng/dL, female; <=45.0, or >45.0 ng/dL) at baseline, VEGF (<38.3, or ≥38.3 mg/dL) at baseline
Multiple linear regression	Absolute value of BCVA (letters) at Month 12	FAS as observed / FAS (LOCF)	Same as above
Multiple linear regression	Number of ranibizumab injections from baseline to Month 11	FAS as observed	Same as above

2.15 Interim analysis

Not applicable.

3 Sample size calculation

In order to detect a clinically meaningful difference in the number of injections (at least 2 injections) at Month 11, as suggested by the principal investigators, this study will randomize at least 56 patients (28 per arm).

For the sample size calculation, we will assume a difference between arms of 2 injections and a standard deviation (SD) of 2.32 (based on CAVNAV study (Liegl et al. 2014)). Based on the non-parametric Wilcoxon-Mann Whitney test for the difference in means this would require 25 patients per arm with 80% power and a 0.025 significance level (1sided), however assuming approximate 10% drops out rate, a total of at least 56 patients (28 per arm) are required to be randomized.

Approximately 70 patients will need to be screened in order to have at least 56 patients eligible and commencing treatment in the trial.

All sample size calculations performed using EAST 6.0.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Imputation for incomplete or missing dates

Adverse events start dates

Adverse events 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 adverse event 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.

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

	Day	Month	Year
Partial Adverse Event 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) = 01JULYYYY 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

5.1.3 Concomitant medication date imputation

5.1.3.1 Start Date Imputation

In order to classify a medication as prior and 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.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(C) Uncertain	(C) Uncertain	(C) Uncertain	(C) Uncertain
YYYY < TRTY	(D) = 01JULYYYY 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	No convention
(A) Before Treatment Start	15MONYYYY
(B) After Treatment Start	MAX(01MONYYYY, TRTSTD+1)
(C) Uncertain	TRTSTD - 1
(D) Before Treatment Start	01JULYYYY
(E) After Treatment Start	01JANYYYY

5.1.3.2 End Date Imputation

1. If the CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date is set to NULL.

2. Else, if the CM end date month is missing, the imputed end date should be set to the earliest of the (End of Study date, 31DECYYYY, date of death).
3. If the CM end date day is missing, the imputed end date should be set to the earliest of the (End of Study date, last day of the month, date of death).
4. If the imputed CM end date is less than the existing CM start date, use the CM start date as the imputed CM end date.

5.1.3.3 Prior therapies date imputation

Not applicable.

5.1.3.4 Post therapies date imputation

Not applicable.

5.1.3.5 Visit Windows

Table 5.1-1 Visit Windows

Visit number	Visit name	Scheduled visit day	Visit window (study days)
1	Screeing	Day -30 to Day -1	
2	Baseline / Day 1	1	1
3	Month 1	30	15 – 44
4	Month 2	60	45 – 74
5	Month 3	90	75 – 104
6	Month 4	120	105 – 134
7	Month 5	150	135 – 164
8	Month 6	180	165 – 194
9	Month 7	210	195 – 224
10	Month 8	240	225 – 254
11	Month 9	270	255 – 284
12	Month 10	300	285 – 314
13	Month 11	330	315 – 344
14	Month 12	360	345 – 374

5.1.3.6 Study observation period definitions

The start and end of the study observation period for non-ocular, study eye, fellow untreated eye, and fellow treated eye are presented in Table 2.

Table 5.1-2 Study Observation Period

Assessment	Period Start	Period End
Non-ocular	date of first treatment (or treatment decision) in the study eye for periods beginning at Day 1 or	data cut-off date for the given analysis period end (Month 12)

Assessment	Period Start	Period End
	date of first ranibizumab injection in the study eye for laser monotherapy patients for the Post first ranibizumab injection to Month 12 Period	
Study eye	date of first treatment (or treatment decision) in the study eye for periods beginning at Day 1 or date of first ranibizumab injection in the study eye for laser monotherapy patients for the Post first ranibizumab injection to Month 12 Period	data cut-off date for the given analysis period end (Month 12)
Fellow eye which never receives treatment		
Fellow untreated eye	date of first treatment in the study eye for periods beginning at Day 1	data cut-off date for the given analysis period end (Month 12)
Fellow eye which receives at least one study treatment		
Fellow untreated eye	date of first treatment in the study eye for periods beginning at Day 1	The earlier date of (the date of first treatment in the fellow eye or the date of the data cut-off for the given analysis period end (Month 12.)
Fellow treated eye	date of first treatment in the fellow eye for periods beginning at Day 1	data cut-off date for the given analysis period end (Month 12)

- For non-ocular, study eye, and fellow untreated eye study observation periods, assessments, regardless of anatomical site, assessments occurring on the date of first treatment in the study eye will not be included in the study observation period unless an adverse event or a post study treatment assessment (e.g., post injection IOP.) Observations occurring on the date of the data cut-off will be included as detailed in the data selection section.
- Assessments occurring in the fellow eye on the date of first treatment in the fellow eye will not be included in the study observation period for the fellow treated eye unless an adverse event or a post study treatment assessment (e.g., post injection IOP.) Observations occurring in the fellow eye on the date of the data cut-off will be included as detailed in the data selection section.
- Non-ocular and study eye assessments occurring on the date of first ranibizumab injection in the study eye for laser monotherapy patients will be included in the study observation period for post first ranibizumab injection to Month 12 Period as detailed in the data selection section.

5.2 AEs coding/grading

The verbatim term recorded on CRF will be identified as adverse event and will be coded by primary system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 21.1 and above.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

The statistical hypothesis testing of the number of ranibizumab treatments will be based on a stratified Cochran-Mantel-Haenszel (CMH) test the observed values as scores and the row mean scores statistic. Stratification will be done based on categories of baseline decimal BCVA (<0.3, or ≥ 0.3, equivalent to 0.52 in logMAR). Difference of mean number of injections, 95% confidence interval (CI) of difference will be done by two sample t-test and one-sided p-value (Score=Table in SAS) of the CMH test will be reported.

The SAS code for CMH test is:

For summary

```
proc univariate data=getstats noprint;
        var nraninj;
        by  trtm24n;
        output out=basestat1 n=N mean=Mean std=SD stdmean=SE median=Median min=Min
max=Max q1=q1 q3=q3 ;
run;
```

For ttest and 95% CI of difference

```
proc ttest data=abcva2 alpha=0.05 order=data;
        class trtm24n;
        var nraninj;
  ods output statistics=diffmean(where=(upcase(class)='DIFF (1-2)')
      keep=class mean lowerclmean upperclmean stderr);
run;
```

For CMH p-value: ANOVA

(For CMH non-parametric: scores=rank should be used)

```
proc freq data=abcva2;
        table bcvagrp*trtm24n*nraninj/cmh2;
```

ods output cmh=pval(where=(althypothesis='Row Mean Scores Differ')/*keep=class mean lowerclmean upperclmean*/) scores=table;

run;

For converting two sided to one sided p-value

```
data pval_(drop=prob rename=(prob_=prob));
        set pval;
        if &mean. < 0 then prob_=prob/2;
        else if &mean. > 0 then prob_=1-(prob/2);
run;
```

5.4.2 Key secondary analysis

Not applicable

5.4.3 Secondary analysis

BCVA

The mean change in BCVA at Month 6 and Month 12 will be compared to Baseline (Day1) using decimal chart (converted to logMAR) and ETDRS (at Month 6, and Month 12) between the 2 treatment arms. The analyses at each visit will be based on an analysis of variance (ANOVA) model with treatment group, and stratification factors. Stratification will be done based on categories of baseline decimal BCVA (<0.3, or ≥0.3, which is translated to 58 letters in ETDRS or 0.52 in logMAR).

SAS code is as follows:

Change from baseline (similar code for average change from baseline for both BCVA or CSFT). For visit, include visit in the model factor

```
proc mixed data = _sub;
   class TRTM24N BCVAGRP;
   model BCVACHG. = TRTM24N BCVAGRP;
   lsmeans TRTM24N/ pdiff  CL alpha = 0.05 OM; *all other stats for lsmeans;
run;
```

5.5 Rule of exclusion criteria of analysis sets

Table 5.1-3 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
I01a	Informed consent taken from subject has date missing or partial.	EXCLUDE FROM FAS AND SAF	3
I01b	Informed consent taken from subject is after Visit 1.	EXCLUDE FROM FAS AND SAF	3
I01c	Informed consent not obtained from the subject or is missing or has no signatures.	EXCLUDE FROM FAS AND SAF	3
I02	Male or female patients less than 20 years of age.	INCLUDE IN EVERYTHING	0
I03	Diagnosis of visual impairment is not exclusively due to ME secondary to BRVO.	EXCLUDE FROM PPS	4
I04	BCVA score at Screening and Baseline (Day 1) is not within the acceptable range of the protocol i.e. outside 0.5 to 0.05 decimal (or 73 to 19 letters EDTRS or 0.3 to 1.30 logMAR).	EXCLUDE FROM PPS	4
I05	Difference between screening and baseline BCVA gain is more than 0.2 units logMAR conversion inclusively from screening to baseline and/or it is more than upper limit (0.3 units logMAR).	INCLUDE IN EVERYTHING	0
I06	Central subfoveal thickness measured by SD-OCT at Baseline (Day 1) is less than or equal to 300μm for study eye.	INCLUDE IN EVERYTHING	0
I07	Duration of vision deterioration more than 6 months (determined by self-report) at screening.	EXCLUDE FROM PPS	4
E01	Patient cannot comply with study or follow-up procedures	INCLUDE IN EVERYTHING	0
E02	Patient is Pregnant at screening or became pregnant during the study participation	INCLUDE IN EVERYTHING	0
E03	Patient is nursing (lactating) at screening or Baseline (Day 1)	INCLUDE IN EVERYTHING	0
E04	Patient has systemic disease/treatment, including any medical condition at screening or baseline which is prohibited as per exclusion criteria point 4.	INCLUDE IN EVERYTHING	0
E05	Patient has history of malignancy of any organ system, treated or untreated, within the past 5 years from screening, regardless of whether there is evidence of local recurrence or metastases.	INCLUDE IN EVERYTHING	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
E06	Patient suffered from stroke or myocardial infarction less than 3 months to Screening	EXCLUDE FROM PPS	4
E07	Patient has uncontrolled blood pressure defined as systolic value of >160 mm Hg or diastolic value of >100 mm Hg (mean of the 3 measurements) at Screening or Baseline (Day 1)	INCLUDE IN EVERYTHING	0
E08	Patient has known hypersensitivity to ranibizumab or any component of the ranibizumab formulation, or fluorescein at screening or Baseline (Day 1)	INCLUDE IN EVERYTHING	0
E09	Patient has any active periocular or ocular infection or inflammation in any of the eye at the time of Screening or Baseline (Day 1).	EXCLUDE FROM PPS	4
E10	Uncontrolled glaucoma (intraocular pressure (IOP) ≥30 mm Hg on medication or according to investigator's judgment) at the time of Screening or Baseline (Day 1)	EXCLUDE FROM PPS	4
E11	Fundus photographs or fluorescein angiograms of sufficient quality cannot be obtained for any of the eye at screening or Baseline (Day 1)	INCLUDE IN EVERYTHING	0
E12	Patient has disease(s) listed in exclusion criteria 12 at the time of screening or Baseline and is continuing in the study.	INCLUDE IN EVERYTHING	0
E13	Patient has substantial cataract in study eye at the time of screening or Baseline (Day 1) that, in the opinion of the investigator, is likely to be decreasing VA by 3 lines or more.	EXCLUDE FROM PPS	4
E14	Patient has Brisk afferent pupillary defect in study eye at the time of screening or Baseline (Day 1).	INCLUDE IN EVERYTHING	0
E15	Patient has Neovascularization of the iris or neovascular glaucoma in study eye at the time of screening or Baseline (Day 1).	EXCLUDE FROM PPS	4
E16	Patient has Vitreomacular traction in study eye at the time of Screening or Baseline (Day 1).	INCLUDE IN EVERYTHING	0
E17	Patient has structural damage in study eye within 0.5 disc diameter of the center of the macula at the time of screening or Baseline (Day 1).	EXCLUDE FROM PPS	4
E18	Patient has history of herpetic ocular infection or ocular toxoplasmosis in study eye at the time of screening or Baseline (Day 1).	INCLUDE IN EVERYTHING	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
E19	Patient has history of idiopathic central serous chorioretinopathy in study eye at the time of screening or Baseline (Day 1).	INCLUDE IN EVERYTHING	0
E20	Patient received other investigational drugs within 30 days or 5 half-lives of Baseline (Day 1), whichever is longer	INCLUDE IN EVERYTHING	0
E21	Patient received any systemic anti-VEGF drugs within 6 months before Baseline (Day1) (e.g., sorafenib (Nexavar®), sunitinib (Sutent®), bevacizumab (Avastin®), ziv-aflibercept (ZALTRAP®)).	INCLUDE IN EVERYTHING	0
E22	Patient is on systemic medications at the time of screening/baseline or plan to use during study period (toxic for lens, retina or optic nerve)	INCLUDE IN EVERYTHING	0
E23	Patient is on treatment with any anti-angiogenic drugs within 3 months before Baseline (Day1) in fellow eye or before Baseline (Day 1) in the study	INCLUDE IN EVERYTHING	0
E24	Patient received pan-retinal laser photocoagulation in study eye within 1 month from Baseline (Day1) or anticipated or scheduled within the next 12 months (Study periods) following Baseline (Day1).	EXCLUDE FROM PPS	4
E25	Patient received any focal or grid laser photocoagulation in study eye before Baseline (Day1).	EXCLUDE FROM PPS	4
E26	Patient underwent any intraocular procedure in the study eye within 2 months from Baseline (Day1) or anticipated within the next 12 months following Baseline (Day1).	INCLUDE IN EVERYTHING	0
E27	Patient with topical ocular in study eye or systemic corticosteroids administered for at least 30 consecutive days within 6 months from Screening	INCLUDE IN EVERYTHING	0
E28	Patient used intra- or periocular corticosteroids (including sub-Tenon) in study eye within 3 months from Screening.	INCLUDE IN EVERYTHING	0
E29	Patient with any use of intraocular corticosteroid implants (e.g., dexamethasone (Ozurdex®), fluocinolone acetonide (Iluvien®)) in study eye.	INCLUDE IN EVERYTHING	0
E30	Patient has history of optic neurotomy, sheathotomy, or filtration surgery at any time in the study eye	INCLUDE IN EVERYTHING	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
E31	Patient has Macular BRVO in study eye.	INCLUDE IN EVERYTHING	0
S01	Treatment of the fellow eye with ranibizumab performed on the same day as treatment of the study eye with ranibizumab.	INCLUDE IN EVERYTHING	0
S02	The minimum gap between 2 injections of ranibizumab should not be less than 23 days.	INCLUDE IN EVERYTHING	0
S03	The minimum gap between 2 laser treatment should not be less than 23 days.	INCLUDE IN EVERYTHING	0
S04	Repeat ophthalmoscopy not performed prior to treatment of the eye if visit assessments and study treatment are on separate dates	INCLUDE IN EVERYTHING	0
S05	Ranibizumab treatment not withheld until next protocol visit after a decrease in BCVA of ≥ 0.6 units in logMAR compared to the last VA assessment.	INCLUDE IN EVERYTHING	0
S06	Ranibizumab treatment not withheld until next protocol visit in case of pre-treatment IOP ≥ 30 mm HG	EXCLUDE FROM FAS AND SAF (from this date)	3
S07	Ranibizumab treatment not withheld until next protocol visit in presence of retinal break	EXCLUDE FROM FAS AND SAF (from this date)	3
S08	Laser treatment not withheld until next protocol visit in absence of macular edema	EXCLUDE FROM FAS AND SAF (from this date)	3
S09	Initial laser treatment not withheld until resolution of dense macular hemorrhage and/or severe retinal edema	EXCLUDE FROM FAS AND SAF (from this date)	3
S10	Laser applied less than 30 minutes prior to injection	INCLUDE IN EVERYTHING	0
S11	Laser is performed more than 14 days after ranibizumab injection at the same month	INCLUDE IN EVERYTHING	0
S12	Re-treatment of ranibizumab injection given without fulfilling the re-treatment criteria or when stabilization criteria was met	EXCLUDE FROM PPS	4
S13	Re-treatment with ranibizumab injection not given although re-treatment criteria was matching or stabilization criteria was not matching	EXCLUDE FROM PPS	4
S14	Post Injection safety assesments and follow ups not performed after ranibizumab treatment	INCLUDE IN EVERYTHING	0

Deviation ID	Description of Deviation	Exclusion in Analyses	Severity code
S15	Ranibizumab treatment not withheld until next protocol visit in case of performed or planned intraocular surgery within the previous or next 28 days	EXCLUDE FROM PPS	4
S16	Treatment Given does not match treatment allocted by NIRT	INCLUDE IN EVERYTHING	0
S17	Visual Acuity examiner is not masked to Randomization treatment	EXCLUDE FROM PPS	4
S18	Re-treatment of laser given without fulfilling the re-treatment criteria or when stabilization criteria was met	EXCLUDE FROM PPS	4
S19	Re-treatment of laser not given although re-treatment criteria was matching or stabilization criteria was not met.	EXCLUDE FROM PPS	4
S20	Laser treatment not withheld until next protocol visit in case of significant increase in macular ischemia as judged by the investigator	EXCLUDE FROM PPS	4
S21	Post laser safety assessments and follow ups not performed after laser treatment	INCLUDE IN EVERYTHING	0
D01	Study treatment has not been discontinued after observing adverse event relating to Rhematogenous retinal detachment.	EXCLUDE FROM FAS AND SAF (from this date)	3
D02	Study treatment has not been discontinued after observing adverse event relating to stage 3 or 4 macular hole.	EXCLUDE FROM FAS AND SAF (from this date)	3
D03	Study treatment has not been discontinued after observing adverse event relating to Stroke or transient ischemic attack (TIA).	EXCLUDE FROM FAS AND SAF (from this date)	3
D04	Study treatment has not been discontinued after patient became pregnant during the course of the study	INCLUDE IN EVERYTHING	0
D05	Prohibited medications / lasers / procedures / surgeries listed in protocol are administered during course of the study however, patient is not discontinued from study treatment and/or study	EXCLUDE FROM FAS AND SAF (from this date)	3

Table 5.1-4 Analysis set exclusions based on severity codes

Analysis set	Severity codes that cause a subject to be excluded
RAN	NA
SAF	2, 3, 6
FAS	1, 3
PPS	4, 6

Table 5.1-5 Severity code text

Severity Code	Severity Code text
0	INCLUDE IN EVERYTHING
1	EXCLUDE FROM FULL ANALYSIS SET (FAS)
2	EXCLUDE FROM SAFETY SET (SAF)
3	EXCLUDE FROM FAS AND SAF
4	EXCLUDE FROM PER-PROTOCOL SET (PPS)
6	EXCLUDE FROM SAF AND PPS

6 Reference

Kriechbaum K, Prager F, Geitzenauer W, Benesch T, Schütze C, Simader C, Schmidt-Erfurth U. (2009) Association of retinal sensitivity and morphology during antiangiogenic treatment of retinal vein occlusion over one year. Ophthalmology; 116(12):2415-21.