NOVARTIS

Clinical Development

RTH258/Brolucizumab

CRTH258AUS04 (MERLIN) / NCT03710564

A multicenter, randomized, double-masked Phase 3a study to assess safety and efficacy of brolucizumab 6 mg q4 weeks compared to aflibercept 2 mg q4 weeks in patients with neovascular age-related macular degeneration (nAMD) with persistent retinal fluid (MERLIN)

Statistical Analysis Plan (SAP)

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23-Apr-2021	*Prior to DB lock*	*Added new categories for shortest and longest time between injections.* *Account for potential non-convegence of repeated measures ANOVA model.* *Clarified the analysis and model used for change from baseline in CST at Week 52* *Changed the explanatory variables used in the model.* *Added detail on ANCOVA model used for the change in CST* *Clarify factors included in logistic regression model for the secondary analysis.* *Changed "study termination"to "study treatment discontinuation" in*	*Amendment 2.0 approved in the documentation system.*	*Section 2.4.1* *Section 2.5.4* *Section 2.7.2.1* *Section 5.4.2* *Table 5-2*

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		description of analysis restrictions.		
28-Apr-2021	*Prior to DB lock*	*Clarification added to presentation of TFLs. "started before the Week 56 visit (i.e., the next scheduled visit after Week 52)" To "started before the date of next scheduled visit after Week 52"*	*Ammendment 3.0 approved in the documentation system*	*Section 2.14*
[redacted]				

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List of abbreviations

ACR	Albumin-Creatinine
[redacted]	[redacted]
AE	Adverse event
A/G	Albumin/Globulin (ratio)
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMD	Age-related Macular Degeneration
ANOVA	Analysis of Variance
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
Bid	bis in diem/twice a day
BCVA	Best-Corrected Visual Acuity
BL	Baseline
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CI	Confidence Interval
cm	Centimeter(s)
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CST	Central Subfield Thickness
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database lock
DMC	Data Monitoring Committee
EDC	Electronic Data Capture
EoS	End of Study
ESI	Event(s) of Special Interest
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAF	Fundus Autofluorescence
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
GGT	Gamma-glutamyl Transferase
HA	Health Authority
HCG	Human Chorionic Gonadotropin
eCRF	Electronic Case Report Form
ICF	Informed Consent Form
IgG	Immunoglobulin G
IOI	Intra-ocular Inflammation

IOP	Intra-ocular Pressure
IP	Investigational Product
IRE	Intra-retinal Edema
IRF	Intra-retinal Fluid
IRT	Interactive Response Technology
IVR	Interactive Voice Response
IWR	Interactive Web Response
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	Milligram(s)
mL	Milliliter(s)
mm	Millimeter(s)
mmHg	Millimeter(s) Mercury
nAMD	Neovascular Age-Related Macular Degeneration
NCI	National Cancer Institute
OCT	Optical Coherence Tomography
[redacted]	[redacted]
o.d.	Once Daily
OS	Overall Survival
PCR	Protein-Creatinine Ratio
PD	Protocol Deviation
PED	Pigment Epithelial Detachment
PFS	Progression-Free Survival
pH	Potential Hydrogen
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
Qd	once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RBC	Red Blood Cell(s)
RECIST	Response Evaluation Criteria in Solid Tumors
RPE	Retinal Pigment Epithelium
RVO	Retinal Vein Occlusion
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD-OCT	Spectral Domain Optical Coherence Tomography
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
SRF	Sub-retinal Fluid

SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
ULN	Upper Limit of Normal
TFLs	Tables, Figures, Listings
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White Blood Cell(s)
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of statistical analyses planned in the study protocol, and to provide detailed statistical methods that will be used for the Clinical Study Report (CSR) of the study CRTH258AUS04.

Data will be analyzed according to the data analysis Section 12 of the study protocol which will be available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details will be provided, as applicable, in Appendix 16.1.9 of the CSR.

This SAP is specifying all the all analyses planned supporting two clinical study reports: one based on an interim analysis based on up to 52 weeks data and another on a final analysis of 104 weeks data. The primary time point for analysis of efficacy and safety data is Week 52. Analysis at other time points will be considered as supportive or supplemental.

The SAP will be finalized before treatment unmasking at the time of the Week 52 database lock (DBL) for the primary analysis. Any changes to the SAP after approval will be documented.

1.1 Study design

This is a multi-center, randomized, double-masked, parallel group study in subjects with neovascular age-related macula degeneration (nAMD). This study has two masked arms wherein subjects will be randomized with a 2:1 (brolucizumab:aflibercept) ratio.

All participants will have study visits every 4 weeks through Week 104. The primary analysis of efficacy and safety data will be performed at Week 52 (Figure 1-1).

Screening Period

Subjects will be screened for enrollment into the double-masked treatment period at the Screening Visit. The screening period may last up to 14 days prior to administration of the first dose of study treatment, dependent upon confirmation of the subject meeting eligibility criteria. Screening must occur between 21 and 31 days from the subject's last Standard of Care (SOC) anti-VEGF injection.

Double-Masked Treatment Period

Subjects meeting eligibility criteria will enter the treatment period and be randomized into one of the following 2 masked treatment arms at the Baseline visit:

- **Masked Arm 1: Brolucizumab 6 mg q4 weeks**

  Brolucizumab 6 mg will be injected every 4 weeks up to and including Visit 26 (Week 100).

- **Masked Arm 2: Aflibercept 2 mg q4 weeks**

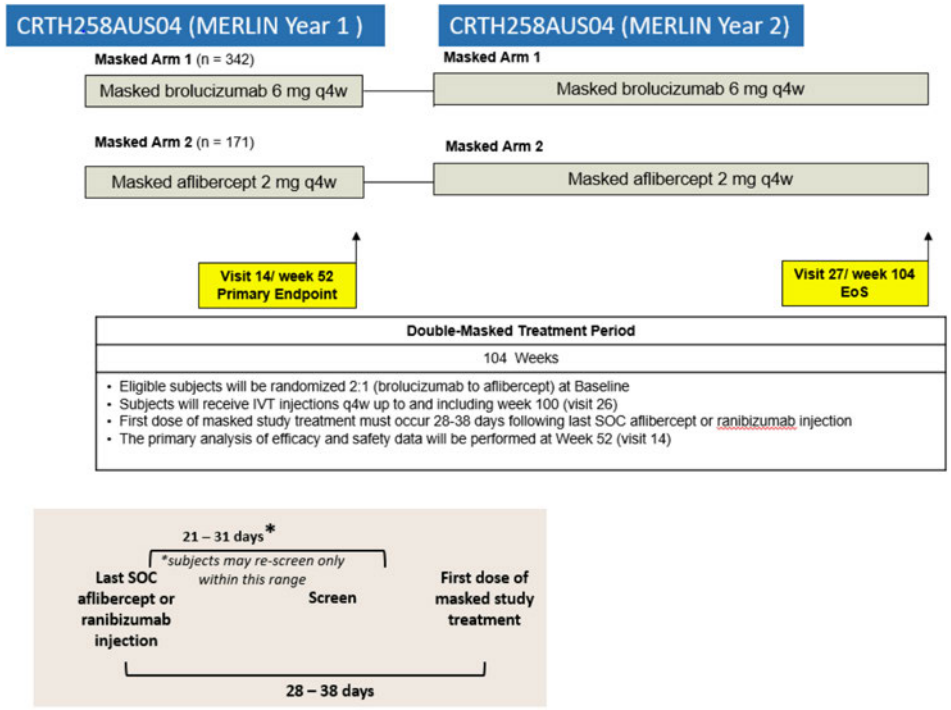
  Aflibercept 2 mg will be injected every 4 weeks up to and including Visit 26 (Week 100).

The first dose of masked study treatment must be administered between 28 and 38 days from the subject's last SOC anti-VEGF injection.

The primary endpoint will be evaluated at Week 52, using data up to and including Week 52. For final data, all data up to and including Week 104 will be used.

Including the Screening Period, the total study duration for a subject may be up to 106 weeks.

Figure 1-1 Study design



1.1.1 Masking

This is a double-masked study, with subjects randomized to be treated with brolucizumab 6 mg q4w or aflibercept 2 mg q4w.

For the purpose of the Week 52 primary analysis, certain team members will be unmasked after the Week 52 database lock to review data and to perform data analysis. These team members will not be involved in subject-level data review during the second year of the study.

1.2 Study objectives and endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate whether brolucizumab 6 mg dosed every 4 weeks is non-inferior at Week 52 to aflibercept 2 mg dosed every 4 weeks	• Change in BCVA from Baseline to Week 52
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**

• To assess efficacy of brolucizumab 6 mg dosed every 4 weeks compared with aflibercept 2 mg dosed every 4 weeks with respect to visual acuity (VA) stabilization or improvement at Weeks 52 and 104 • To evaluate anatomic parameters of disease activity and retinal fluid status in subjects treated with brolucizumab 6 mg dosed every 4 weeks compared with aflibercept 2 mg dosed every 4 weeks • To assess safety and tolerability of brolucizumab 6 mg dosed every 4 weeks compared with aflibercept 2 mg dosed every 4 weeks	Efficacy Endpoints • VA stabilization or improvement at Week 52 and Week 104 • Loss in BCVA of 5/10/15 letters or more from Baseline to each post-baseline visit • Gain in BCVA of 5/10/15 letters or more from Baseline to each post-baseline visit • Change in central subfield thickness (CST) from Baseline to each post-baseline visit • Absence of IRF and/or SRF at each post-baseline visit • Absence of sub-RPE fluid in subjects with sub-RPE fluid at Baseline • Fluid free status- no IRF and no SRF at each post-baseline treatment visit • Fluid free status- no IRF, no SRF and no sub-RPE fluid at each post-baseline treatment visit • Time to first dry retina (no IRF and no SRF) • Time to first dry retina (no IRF, no SRF, and no Sub-RPE) • Time to sustained dry retina (no IRF and no SRF at ≥ 2 consecutive visits) • Time to sustained dry retina (no IRF and no SRF and no Sub-RPE at ≥ 2 consecutive visits) [redacted] Safety and Tolerability Endpoints • Incidence of treatment-emergent Adverse Events (AEs) • Treatment-emergent changes in ocular and systemic parameters

[redacted]

2 Statistical methods

2.1 Data analysis general information

The primary safety and efficacy analysis will be based on the Week 52 data, i.e. all data up to and including Week 52. This analysis will be performed when all randomized subjects have completed their Week 52 visit or terminated the study before Week 52. The final analyses will include all data through Week 104.

The statistical analysis will be performed by Novartis (NBS CONEXTS). Analysis datasets and statistical outputs will be produced using the SAS® Version 9.4 or higher and stored in Novartis global programming & statistical environment (GPS II).

Tables will be presented based on the unit subject, with ocular parameters presented separately for the study- and fellow-eye as applicable.

Continuous variables will be summarized using the number of observations, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, interquartile range, and maximum values. Categorical variables will be summarized with frequencies and percentages. Where appropriate, 2-sided 95% confidence intervals (CIs) for point estimates of the mean or proportion will be provided. For the treatment difference brolucizumab - aflibercept, point estimates and 95% CIs will be provided as appropriate unless otherwise specified.

Outputs will be presented by treatment. Listings will include the following identifying variables: treatment, center, subject, age, sex, and race. In addition, ocular assessments will include identification of the study and fellow eye.

2.1.1 General definitions

Treatment refers to both brolucizumab 6 mg and aflibercept 2 mg IVT injections.

The **Baseline** value for efficacy and safety variables is the last available value collected prior to the first treatment which can occur at the Baseline or Screening visits.

All data collected after the first study treatment are defined as post-Baseline.

Day 1 is defined as the date of first dose of study drug (brolucizumab or aflibercept). Study day is defined as the number of days relative to the date of first dose of study treatment (Day 1).

The **study day** for a scheduled or unscheduled visit on or post Baseline is defined as:

Study day = (date of visit) – (date of first study treatment) + 1

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

Study day = (date of visit) – (date of first study treatment)

Unscheduled visits:

All data collected at unscheduled visits will be included in listings. In data analyses, inclusion or exclusion of assessments obtained from unscheduled visits will be specified in the corresponding sections.

Study eye:

In cases where both eyes are eligible, the eye with the worse BCVA at Baseline will be selected as the study eye. If both eyes have the same BCVA, it is recommended to select the right eye as the study eye.

2.2 Analysis sets

The **Randomized Analysis Set (RAS)** consists of all randomized subjects. This analysis set will be used to describe the randomized subjects by treatment group with respect to demographics and Baseline characteristics.

The **Full Analysis Set (FAS)** comprises all subjects to whom study treatment has been assigned by randomization. According to the intent-to-treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure. This analysis set will be used for all efficacy analyses, if not otherwise specified.

The **Per-Protocol Set (PPS)** defined for the primary efficacy analysis at Week 52 includes all subjects in the FAS with no protocol deviations that are expected to majorly affect the assessment of efficacy at Week 52 including: lack of compliance (including treatment misallocation), missing data, concomitant medication and deviation from inclusion/exclusion criteria. Discontinuation from treatment due to lack of efficacy and/or safety does not constitute a reason for exclusion from PPS.

The **Safety Analysis Set (SAF)** includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the first study treatment received if the randomized treatment was never received. All safety analyses will be based on the SAF.

Before the Week 52 and Week 104 database lock the relevant protocol deviations will be identified at the subject level in the database, prior to unmasking (for Week 52 analysis), analysis restrictions (ARs) will be derived in the analysis database. Censoring applied in relation to the specific PDs / ARs will be specified as well.

Rules of exclusion criteria of analysis sets are defined in Appendix 5.5.

2.2.1 Subgroups of interest

The subgroups of interest are listed below:

- Subjects with Baseline BCVA 20/40 or worse (<= 70, >= 71 letters)
- Most recent prior anti-VEGF treatment (aflibercept or ranibizumab)
- Time since first anti-VEGF injection (≤ 36 months, > 36 month)
- Age category (< 75 years and ≥ 75 years)
- Gender (male, female)
- AESI (yes, no)

Impact of COVID-19 pandemic:

As per internal guidance, a sensitivity analysis related to the exposure of subjects to COVID-19 will be conducted. The definition of start and end dates by geographical areas to be used for the sensitivity analysis for the USA has been 01-Mar-2020.

Non-exposed subjects to COVID-19 are defined as subjects who:

- completed Week 52 visit prior to pandemic start date,
- or withdrew study prior to pandemic start date,
- or withdrew treatment and started alternative anti-VEGF treatment prior to pandemic start date.

Exposed subjects to COVID-19 are therefore defined as subjects who:

- did not complete Week 52 visit prior to pandemic start date (while remaining in the study at the time of pandemic start date),
- or withdrew study on or after pandemic start date,
- or withdrew treatment and started alternative anti-VEGF treatment on or after pandemic start date.

2.3 Patient disposition, demographics and other baseline characteristics

Subject characteristics and study conduct summaries include tables and listings such as a subject disposition table, demographics and baseline characteristics tables, listing of treatment assignment by investigator, summary of screen failures by reason and listing of subjects excluded from the FAS, PPS and SAF including the corresponding reasons.

2.3.1 Patient disposition

Subject disposition table will be based on the randomized analysis set. The following summaries will be included in the disposition table: number and percent of subjects who were randomized and treated (= received at least one injection), completed the study (Week 52/Week 104), discontinued from treatment / study overall, and by reason of discontinuation from treatment / study overall. Percentages will be based on the number of subjects who are randomized.

A subject is considered to have completed one year (Week 52) if he/she did not discontinue study prior to the Week 52 visit. Discontinuation at Week 52 with exit visit assessment performed is considered as ‘completed year one’ for the Week 52 analysis.

A subject is considered to have completed the study (Week 104) if he/she did not discontinue study prior to the Week 104 visit. Discontinuation at Week 104 with exit visit assessment performed is considered as ‘completed’ for the Week 104 analysis.

Subjects who sign an informed consent form and who are subsequently found to be ineligible prior to randomization will be considered a screen failure. Number and percent of subjects who are screen failures (i.e. were not randomized) will be presented. A listing of all screen failures along with the corresponding reason will be presented.

Number and percent of subjects who were excluded (i.e. not evaluable) from each of the SAF, FAS, and PPS will be presented using the randomized analysis set. A listing of subjects along with the analysis set that they were excluded from and the corresponding reasons will also be presented.

Number and percent of subjects with major protocol deviations and analysis restrictions will be presented by deviation/restriction category. Due to the COVID-19 pandemic, higher number of PDs are expected. To evaluate the PDs that occurred due to COVID-19, the number and percentage of subjects with PDs that occurred due to COVID-19 outbreak will also be provided by deviation category and treatment arm. A listing of all relevant deviations will be presented.

A listing of subjects who discontinue from the study and/or treatment early will be provided. The listing will identify when the study or treatment was discontinued including the corresponding reasons.

2.3.2 Demographic and baseline characteristics

Demographic table will include age (both as a continuous variable and using categories (< 75, >= 75 years)), sex, race, ethnicity. Demographic summary tables will be listed and summarized descriptively by treatment group for the RAS, FAS, and SAF.

Baseline characteristics table will include: Japanese ancestry, study eye, iris color, history of primary diagnosis, time since first anti-VEGF injection (≤ 36 months or > 36 months), and most recent anti-VEGF treatment (aflibercept or ranibizumab), BCVA (both as a continuous variable and using categories (<= 70, >= 71)) using the ETDRS visual acuity, area of CNV, CST as continuous variable and categorical (< 400uM, >= 400uM), presence of IRF, SRF and sub-RPE fluid, presence of RAP lesions. The baseline characteristics table will be presented separately for the study and fellow eye.

Demographic characteristics and other baseline characteristics will be presented and summarized with appropriate descriptive statistics for the RAS, FAS, and SAF.

If imbalance between treatment groups with respect to some variables occurs, supplemental analyses of variance/covariance with addition of these variables will be performed to assess the impact on efficacy as appropriate.

A subject listing containing all demographics information by investigator will be presented using the RAS.

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

2.4.1 Study treatment / compliance

Extent of exposure to investigational product is calculated as the number of injections received.

The SAF will be used for the analyses described in this section. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, interquartile range, and maximum will be presented.

The duration of exposure (in days) to study medication, defined as: (Date

of cutoff of safety assessment – Date of first injection) + 1

will be summarized by means of descriptive statistics by treatment group.

In addition, shortest and longest time between injections (days) will be summarized descriptively.

2.4.2 Medical history, and prior/concomitant medication

2.4.2.1 Medical history

Medical history (ocular and non-ocular) will be tabulated by system organ class and preferred term of the MedDRA dictionary using the SAF. Ocular events will be presented separately by study and fellow eye. A listing of all medical history data will be provided.

2.4.2.2 Prior medication

Prior medications (ocular and non-ocular) will be summarized using number and percentage of subjects by ATC class and preferred term according to the WHO Drug Reference List dictionary using the randomized analysis set. Prior medications include medications used (prior to date of first study treatment. Ocular medications will be presented separately for the study and fellow eye. A listing of all prior medications will be provided.

2.4.2.3 Concomitant medication

The number and percentage of subjects taking concomitant medications will be summarized by ATC class and preferred term according to the WHO Drug Reference List dictionary using the SAF. Medications that were taken during the treatment period, including those that started prior to first injection but continued after treatment start, will be summarized as concomitant medications. Concomitant medications will be classified in addition as whether or not they started prior to first IVT injection for ocular conditions, separate summaries will be presented for study and fellow eye. A listing of all concomitant medication will be provided.

2.4.2.4 Concomitant procedures

The number and percentage of subjects who had procedures performed during the study will be summarized by system organ class and preferred term according to the MedDRA dictionary using the SAF. For ocular procedures, separate summaries will be presented for study and fellow eye. A listing of all concomitant procedures will be provided.

2.5 Analysis of the primary endpoint

The primary aim of the study is to evaluate whether brolucizumab 6 mg dosed every 4 weeks is non-inferior to aflibercept 2 mg dosed every 4 weeks based on BCVA assessment at Week 52.

2.5.1 Primary endpoint

The primary efficacy endpoint is change in BCVA from Baseline to Week 52. BCVA will be measured based on the procedures developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) and the results will be reported in letters.

The primary efficacy analysis will be based on the FAS with last-observation-carried-forward (LOCF) imputation of missing or censored BCVA values.

2.5.2 Statistical hypothesis, model, and method of analysis

The objective related to the primary endpoint is to evaluate whether brolucizumab 6 mg dosed every 4 weeks is non-inferior at Week 52 to aflibercept 2 mg dosed every 4 weeks.

Let:

B = Brolucizumab 6 mg

A = Aflibercept 2 mg

The following non-inferiority hypotheses are related to a non-inferiority margin of 4 letters:

$$\mathbf{H_{01}}: \mu_B - \mu_A \leq -4 \text{ letters} \quad \text{vs.} \quad \mathbf{H_{A1}}: \mu_B - \mu_A > -4 \text{ letters}$$

where μ_B and μ_A are the corresponding unknown true mean changes from baseline in BCVA at Week 52.

The primary efficacy analysis will be performed using FAS. An analysis of variance (ANOVA) model with the primary efficacy endpoint as the response variable, and treatment, Baseline BCVA categories (<= 70, >= 71 letters), immediate prior treatment (aflibercept or ranibizumab) and time since first anti-VEGF injection (≤ 36 months, > 36 months), and age categories (< 75, >= 75 years) as factors will be used for the primary efficacy analysis.

Difference in means (brolucizumab q4 week dosing minus aflibercept q4 week dosing) of the primary efficacy endpoint and its two-sided 95% confidence interval (CI) will be calculated using the above-mentioned ANOVA model.

Non-inferiority of brolucizumab 6 mg dosed every 4 weeks to aflibercept 2 mg dosed every 4 weeks will be established if the lower limit of the 95% CI mentioned above is greater than -4 letters (corresponding to the non-inferiority margin of 4 letters).

2.5.2.1 Visit windows

All efficacy variables assessed during **scheduled visits** will be allocated to an analysis visit for the purposes of by-visit analyses or summaries. This allocation follows the principle of using the actual day of evaluation nearest the scheduled time point. If a visit is not on schedule, it will be allocated to the closest visit (except that no post baseline visit would be allocated to the baseline visit). The visit windows for efficacy are described in Table 2-1.

Prior to visit window assignment, all efficacy data will be censored at the time the subject started alternative anti-VEGF treatment in the study eye on or after the discontinuation from study treatment.

All safety assessments (**including unscheduled visits**) will be considered for analysis visit window.

If more than one evaluation of the same endpoint is allocated to an analysis visit, the non-missing evaluation closest to the scheduled visit will be used (if they are equally distanced from the scheduled visit, then the latter non-missing evaluation would be used).

Table 2-1 Analysis visit window

Efficacy variables, vital signs, IOP		
Visit day interval	**Scheduled visit**	**Analysis visit (Target day)**
Up to Day 1	Screening/Visit 1/ Randomization	Baseline (Day 1)
Days 2 – 42	Visit 2/ Week 4	Week 4 (Day 28)
Days 43 – 70	Visit 3/ Week 8	Week 8 (Day 56)
Days 71 – 98	Visit 4/ Week 12	Week 12 (Day 84)
Days 99 – 126	Visit 5/ Week 16	Week 16 (Day 112)
Days 127 – 154	Visit 6/ Week 20	Week 20 (Day 140)
Days 155 – 182	Visit 7/ Week 24	Week 24 (Day 168)
Days 183 – 210	Visit 8/ Week 28	Week 28 (Day 196)
Days 211 – 238	Visit 9/ Week 32	Week 32 (Day 224)
Days 239 – 266	Visit 10/ Week 36	Week 36 (Day 252)
Days 267 – 294	Visit 11/ Week 40	Week 40 (Day 280)
Days 295 – 322	Visit 12/ Week 44	Week 44 (Day 308)
Days 323 – 350	Visit 13/ Week 48	Week 48 (Day 336)
Day 351 – date of Year-1 cutoff day of safety assessment (ifapplicable)	Visit 14/ Week 52	Week 52 (Day 364)
Date of Year-1 cutoff day of safety assessment + 1 – Day 406	Visit 15/Week 56	Week 56 (Day 392)
Days 407 – 434	Visit 16/Week 60	Week 60 (Day 420)
Days 435 – 462	Visit 17/Week 64	Week 64 (Day 448)
Days 463 – 490	Visit 18/Week 68	Week 68 (Day 476)
Days 491 – 518	Visit 19/Week 72	Week 72 (Day 504)
Days 519 – 546	Visit 20/Week 76	Week 76 (Day 532)
Days 547 – 574	Visit 21/Week 80	Week 80 (Day 560)
Days 575 – 602	Visit 22/Week 84	Week 84 (Day 588)
Days 603 – 630	Visit 23/Week 88	Week 88 (Day 616)
Days 631 – 658	Visit 24/Week 92	Week 92 (Day 644)
Days 659 – 686	Visit 25/Week 96	Week 96 (Day 672)

Days 687 – 714	Visit 26/Week 100	Week 100 (Day 700)
Days 715 -	Visit 27/Week 104 (EoS)	Week 104 (Day 728)

[redacted]

Laboratory Variables		
Visit day interval	**Scheduled visit**	**Analysis visit (Target day)**
Up to Day 1	Screening/Visit 1/Randomization	Baseline (Day 1)
Days 2 – 224	Visit 4/Week 12	Week 12 (Day 84)
Days 225 - date of Year-1 cutoff day of safety assessment (if applicable)	Visit 14/Week 52	Week 52 (Day 364)
Date of Year-1 cutoff day of safety assessment + 1 – Day 588	Visit 17/Week 64	Week 64 (Day 448)
Days 589 -	Visit 27/Week 104 (EoS)	Week 104 (Day 728)

2.5.3 Handling of missing values/censoring/discontinuations

The primary presentation of efficacy results will use **LOCF** approach for replacement/imputation of censored/missing values. All non-missing post-Baseline values (excluding assessments done at unscheduled visit) will be used when implementing the LOCF imputation. Baseline values will not be carried forward. For subjects who discontinue

treatment but continue in the study, the efficacy data will be censored at the time the subject started alternative anti-VEGF treatment in the study eye on or after the discontinuation from study treatment. No other censoring is applied within the FAS analysis of the primary endpoint. Censored or missing data will be replaced/imputed by the last observation prior to receiving alternative anti-VEGF treatment.

2.5.4 Sensitivity and Supportive analyses

Sensitivity analyses

A sensitivity analysis to explore impact of protocol deviations on the primary efficacy results at Week 52 will be performed using the PPS with **LOCF** imputation/replacement of missing and censored values using the same model and factors as in the primary efficacy analysis model.

Another sensitivity analysis to explore the robustness of the primary efficacy analysis results related to censored and missing values will be performed by using **observed-case approach** (after censoring rule applied) in the FAS. A repeated measures ANOVA model with the BCVA change from baseline at each scheduled visit up to Week 52 as the response variable, and treatment, week, treatment-by-week interaction, Baseline BCVA categories (<= 70, >= 71 letters), prior treatment (aflibercept or ranibizumab) and time since first anti-VEGF injection (≤ 36 months, > 36 month), and age categories (< 75, >= 75 years) as factors will be employed. An unstructured or compound symmetry covariance matrix for the repeated measures within each subject will be applied in the analysis. The two treatment groups will be compared at Week 52 by reporting a point estimate together with a 95% CI for the treatment difference, based on least squares mean. The SAS® procedure PROC MIXED will be used for the above analyses.

If a repeated measures ANOVA model with an unstructured covariance matrix does not converge, a more restricted covariance matrix can be considered in the following order until convergence is reached: compound symmetry (CS), first-order autoregressive (AR), Toeplitz (TOEP), and variance components (VC).

Supportive analyses

The analyses of change in BCVA from Baseline to Week 52 will be performed by subgroups (see Section 2.2.1).

Analyses will be conducted by fitting the same model as in the analysis of primary endpoint for FAS by subgroup.

2.6 Analysis of the key secondary endpoint(s)

There is no key secondary objective for this study.

2.7 Analysis of secondary and exploratory efficacy endpoints

2.7.1 Secondary endpoints

The secondary efficacy endpoints are the following:

1. VA stabilization or improvement at each post-Baseline visit (Change from baseline > -5 letters, i.e. no worse than 5 letters loss in BCVA compared to Baseline) (yes, no)
2. BCVA >= 84 letters or gain of 15 letters or more in BCVA at each post-Baseline visit (yes, no)
3. BCVA >= 84 letters or gain of 10 letters or more in BCVA at each post-Baseline visit (yes, no)
4. BCVA >= 84 letters or gain of 5 letters or more in BCVA at post-Baseline visit (yes, no)
5. Loss of 5 letters or more in BCVA at each post-Baseline visit (yes, no)
6. Loss of 10 letters or more in BCVA at each post-Baseline visit (yes, no)
7. Loss of 15 letters or more in BCVA at each post-Baseline visit (yes, no)
8. Change in Central Subfield Thickness (CST) from Baseline to each post-Baseline visit
9. IRF (present, absent) at each post-Baseline visit
10. SRF (present, absent) at each post-Baseline visit
11. Sub-RPE fluid (present, absent) at each post-Baseline visit
12. Fluid free (no IRF and SRF) status (yes, no) at each post-Baseline visit
13. Fluid free (no IRF, SRF and sub RPE fluid) status (yes, no) at each post-Baseline visit
14. Time to first dry retina (no IRF and no SRF)
15. Time to first dry retina (no IRF, no SRF, and no Sub-RPE)
16. Time to first sustained dry retina (no IRF and no SRF at ≥ 2 consecutive assessments at least 21 days apart)
17. Time to first sustained dry retina (no IRF, no SRF and no Sub-RPE at ≥ 2 consecutive assessments at least 21 days apart)

2.7.2 Statistical hypothesis, model, and method of analysis

2.7.2.1 Confirmatory testing related to additional secondary efficacy endpoints

Confirmatory hypothesis testing for additional secondary endpoints will be performed in case the proof of non-inferiority related to BCVA is successful for the primary endpoint.

The additional efficacy hypotheses are linked to the below endpoints:

A. Change from Baseline in CST in the study eye at Week 52;

B. Fluid-free (No IRF and no SRF) in the study eye at Week 52 (yes/no).

All tests will be two-sided for superiority of brolucizumab vs aflibercept.

The alternative hypotheses will be tested hierarchically in the order of A, then B, i.e., confirmatory testing of the hypothesis requires rejection of the previous null hypothesis. In this setting, each hypothesis will be assessed at a two-sided significance level of 0.05, while keeping the global type I error rate at 0.05.

The basis for these tests for superiority will be the FAS with LOCF imputation of missing or censored data.

Change from baseline in CST at Week 52 will be analyzed using

an analysis of covariance (ANCOVA) model with the change in CST as the response variable, and treatment, immediate prior treatment (aflibercept or ranibizumab) and time since first anti-

VEGF injection (≤ 36 months, > 36 months), and age categories (< 75, >= 75 years) as factors, and baseline CST as a covariate.

Difference in means (brolucizumab q4 week dosing minus aflibercept q4 week dosing), its two-sided 95% confidence interval (CI), and p-value will be calculated using the above-mentioned ANCOVA model.

The treatment comparison of proportions of subjects with fluid-free (No IRF and no SRF) in the study eye at Week 52 will be based on a marginal standardized method, for which the rate difference will be derived applying the bootstrapping method using a logistic regression model adjusted by treatment and age categories (< 75, >= 75 years).

2.7.2.2 General analysis specifications for secondary efficacy endpoints

No hypothesis will be tested for additional secondary endpoints. All p-values will be considered as nominal.

Other categorical variables will be summarized descriptively by treatment and visit. Difference in proportions of subjects, brolucizumab q4 week dosing aflibercept q4 week dosing, and its two-sided 95% CI, together with the p-values will be calculated using normal approximation or exact method as applicable.

Continuous variable will be analyzed in a similar method as used in the analysis of primary efficacy variable by visit.

Time-to-event variables will be analyzed using Kaplan-Meier method. Proportions of subjects with event will be presented by treatment group and time point, together with 95% CI (using Greenwood's formula). KM curves presenting the cumulative probability of first event will be provided by treatment group, log-rank test will be used for between treatment group comparison.

The time to event will be assessed at the Week 52 analysis and at the end of study analysis. For the Week 52 analysis, patients continuing in the study but without event on or before Week 52 will be censored on the Week 52 cut-off date; patients who discontinued from the study or started alternative anti-VEGF treatment after treatment discontinuation before Week 52 will be censored at the time with the last non-missing assessment after data censoring.

In the analyses of time to event variables, assessments obtained during **unscheduled** visits will also be considered.

2.7.3 Handling of missing values/censoring/discontinuations

Same instructions as for LOCF method using FAS for the primary endpoint, if not otherwise specified.

2.8 Safety analyses

For all safety analyses, the SAF will be used. All listings and summary tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of Baseline data, which will also be summarized where appropriate (e.g. change from Baseline summaries). In addition, a separate listing for death including on-treatment and post

treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

For the primary analyses at Week 52, the on-treatment period lasts from the date of first administration of study treatment to date of Week 52 cut-off date or end of study or start date of alternative anti-VEGF (whichever is earlier), unless otherwise specified.

For the final analyses at Week 104, the on-treatment period lasts from the date of first administration of study treatment to end of study or start date of alternative anti-VEGF (whichever is earlier), unless otherwise specified.

2.8.1 Adverse events (AEs)

Analysis and presentation of AEs occurring during the screening period will be separated from those occurring during the investigational period where a comparative evaluation of treatment-emergent AEs is intended.

A treatment-emergent adverse event (TEAE) is defined as any adverse event that develops after initiation of the study treatment or any event already present that worsens following exposure to the study treatment. Only treatment-emergent adverse events will be presented in the summary tables.

Adverse events will be coded using the MedDRA dictionary and presented by system organ class (SOC) and preferred term (PT). Treatment-emergent AEs will be analyzed based on the number and percentage of subjects with at least one AE in the category of interest.

The number (and proportion) of subjects with TEAEs will be summarized at each analysis in the following ways:

Table 2-2 TEAE summary

TEAE summary	AE categories		
	Ocular AE in the study eye	**Ocular AE in the fellow eye**	**Non-ocular AE**
AEs by treatment, primary SOC and PT	Y#	Y	Y#
AEs by treatment, primary SOC, PT and maximum severity	Y	Y	Y
AEs by treatment, and PT (including events with onset date after start of alternative anti-VEGF treatment)	Y		
AEs by treatment, and PT (events with onset date after start of alternative Anti-VEGF treatment)	Y		
Frequent AEs by PT┼	Y		Y
AEs related to study treatment by SOC and PT	Y	Y	Y
AEs leading to permanent discontinuation of study treatment by SOC and PT	Y	Y	Y
SAEs by treatment, primary SOC and PT	Y	Y	Y
SAEs related to study treatment by SOC and PT	Y		Y
┼≥2 % (or other cutting point as appropriate) in any treatment group for a given PT.			

TEAE summary	AE categories		
	Ocular AE in the study eye	Ocular AE in the fellow eye	Non-ocular AE
# For the subgroup of COVID-19 exposed, and non-exposed as defined in Section 2.2.1			

Subject listings for all AEs, serious AEs, AEs that lead to discontinuation from treatment and/or study, AEs related to study treatment, and AEs of special interest will be presented.

The SOCs will be presented in alphabetical order. Preferred terms will be ordered within each SOC by decreasing incidence in the brolucizumab 6 mg treatment arm. The MedDRA version used for reporting the study will be the latest available prior to the database lock and will be described in a footnote. A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

2.8.1.1 Adverse events of special interest / grouping of AEs

Incidence of adverse events of special interest (AESI) will be tabulated by treatment arm. AESIs will be identified via the RTH258 electronic case retrieval strategy (eCRS). The eCRS that is current at the time the database lock will be used and AESIs will be identified where the flag Core safety topic risk (SP) = 'Y'. A subject listing will also be presented for AESIs. AESIs will be identified by category of interest and presented by category and preferred term. In addition, patient profiles will be prepared for patients with intra-ocular inflammation (IOI) events.

2.8.1.2 Adverse event reporting for clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov (and EudraCT, if applicable), two required tables on TEAEs which are not serious adverse events with an incidence greater than 5% and on TEAEs and SAEs suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for the same subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE (respectively non-SAE) has to be checked in a block e.g., among AEs in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment, and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

This analysis will be part of the end of study (year-2) CSR only.

2.8.2 Deaths

All deaths that occurred during the treatment period will be identified on the AE eCRF page and will be summarized using counts and percentages by system organ class and preferred term according to the MedDRA dictionary. A subject listing will be presented for all deaths including date and cause of death.

2.8.3 Laboratory data

Clinical laboratory evaluations consist of hematology, blood chemistry and urinalysis.

Hematology (Complete Blood Count)

The following hematology parameters will be collected: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute and percentage of neutrophils, lymphocytes, monocytes, eosinophils, basophils and other) and quantitative platelet count.

Observed values and change from baseline values for each hematology parameter will be presented descriptively by visit and treatment group. In addition, descriptive summaries will be presented graphically using boxplots. For the parameters presented in Table 2-3, each value will be categorized as low, not meeting alert criteria, or high using the clinically notable ranges as given in the table. A shift table showing category of each parameter at baseline relative to each post-baseline visit, to the last assessment, to the most extreme increase and most extreme decrease will be presented by treatment group.

A subject listing will be provided for all laboratory data collected. Additional listings for subjects with at least one value satisfying the clinically notable criteria given on Table 2-3 will be presented.

Blood Chemistry

The following blood chemistry parameters will be collected: Blood Urea Nitrogen (BUN) or Urea, Serum Creatinine, BUN/Creatinine ratio, Uric Acid, Cholesterol, Triglycerides, Albumin, Total Globulin, Albumin/Globulin (A/G) ratio, total Serum Iron, total Protein, Serum Electrolytes (Sodium, Potassium, Bicarbonate, Chloride, Calcium, Magnesium), Phosphate, Amylase, Lipase, Glucose (non-fasting), The following liver function tests (LFTs): Aspartate aminotransferase [AST], Alanine aminotransferase [ALT], Alkaline Phosphatase (ALP), Gamma-Glutamyl Transferase (GGT), total Bilirubin, direct Bilirubin, indirect Bilirubin, and Lactate Dehydrogenase (LDH).

The blood chemistry parameters will be analyzed and presented in the same manner as the hematology variables.

Urinalysis

The following urinalysis parameters will be collected: specific gravity, pH, color, protein, glucose, blood, ketones, bilirubin and microscopic examination (WBC, RBC, epithelial cells, bacteria, mucus, casts and crystals).

Two of the urinalysis variables (specific gravity and reaction pH) are continuous variables and will be presented in the same manner as the hematology and chemistry variables. Specific gravity will be represented with 3 decimal places. The remaining variables are categorical and will be presented in shift tables as described above.

Table 2-3 Clinically notable laboratory values

Panel/Test	Type	Gender/ Age	Con-ventional Unit	Con-ventional Low	Con-ventional High	SI Unit	SI Low	SI High	Non-numeric
Chemistry/ Calcium	alert	All	mg/dL	6.1	12.9	mmol/L	1.52	3.22	
Chemistry/ Creatinine	reference	All	mg/dL	0.7	1.4	µmol/L	62	124	
Chemistry/ Glucose (non fasting)	alert	All	mg/dL	40	450	mmol/L	2.22	24.98	
Chemistry/ Potassium	alert	All	mEq/L	2.8	6.3	mmol/L	2.8	6.3	
Chemistry/ Sodium	alert	All	mEq/L	117	160	mmol/L	117	160	
HCG (if applicable)	alert	All							Negative, inconclu-sive
Hematology/ Hematocrit	alert	All	%	18	60	%	18	60	
Hematology/ Hemoglobin	alert	All	g/dL	8	22	g/L	80	220	
Hematology/ Platelet	alert	All	K/cu mm	30	900	x10^9/L	30	900	
Hematology/ WBC	alert	All	K/cu mm	2	25	x10^9/L	2	25	

2.8.4 Other safety data

2.8.4.1 Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available, abnormalities will be flagged. Descriptive statistics will be provided by treatment and visit/time and will be presented graphically.

Descriptive summaries of observed values and change from baseline in each vital sign parameters at each study visit will be presented.

A summary table with counts and percentage of subjects satisfying the criteria given in Table 2-4 will be presented by visit, to the last assessment visit and to at least one visit.

Table 2-4 Clinically notable changes in vital signs

Variable	Category	Critical Values
Systolic blood	High	Either > 180 with an increase from baseline > 30 or > 200 absolute

pressure (mmHg)	Low	Either < 90 with a decrease from baseline > 30 or < 75 absolute
Diastolic blood pressure (mmHg)	High	Either > 105 with an increase from baseline > 20 or > 115 absolute
	Low	Either < 50 with a decrease from baseline > 20 or < 40 absolute
Pulse rate (bpm)	High	Either >120 with an increase from baseline of > 25 or > 130 absolute
	Low	Either < 50 with a decrease from baseline > 30 or < 40 absolute

A subject listing of all vital sign parameters will be presented. In addition, a separate listing for subjects satisfying at least one criterion in Table 2-4 will also be presented.

2.8.4.2 Intra-ocular pressure (IOP) assessment

For both pre-injection and post-injection the number and percentage of subjects with IOP > 30 mmHg at any visit will be summarized.

Post-injection IOP is to be assessed approximately 30-60 minutes after injection and if ≥ 25 mmHg, the assessment should be repeated until back to normal. Summary tables with counts and percentage of subjects with an IOP increase of ≥ 10, ≥ 20 mmHg from pre-injection to post-injection at any visit, and last visit for the study eye will be presented.

For both pre-injection and post-injection a summary table with counts and percentage of subjects with observed IOP ≥ 21mmHg at 3 consecutive scheduled visits will be presented.

A visit with missing pre-injection IOP is considered to meet the ≥ 21mmHg criterion if the preceding and the following visits meet the criterion that pre-injection IOP ≥ 21mmHg. For example, if schedule visit X has missing pre-injection IOP and pre-injection IOP ≥ 21mmHg is observed for both visit X-1 and X+1, the subject is considered to meet the criteria at visit X as well.

A listing for subjects with any post-injection IOP increase of ≥ 10mmHg from pre-injection IOP and a listing of subjects with any IOP > 30mmHg will be presented.

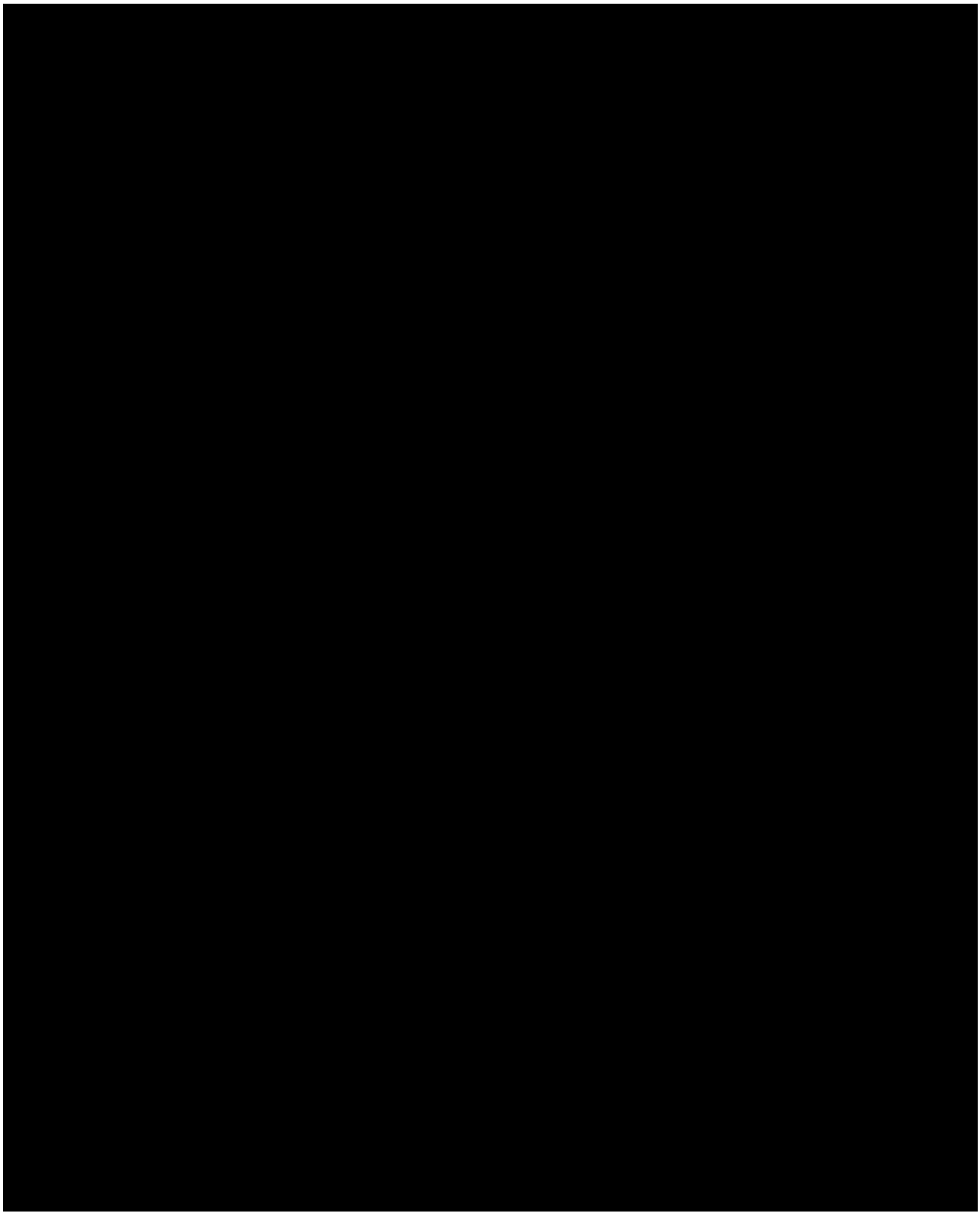
2.8.5 Analysis of Imaging related to intra-ocular inflammation events

Starting approximately after March-2020, additional images were taken in case of intra-ocular inflammation events (section 8.3.2 of the protocol). OCT, color fundus photography and fluorescein angiography (preferably wide-field or with peripheral sweeps) images were assessed by the CRC. In case of event reported outside the scheduled visits, images were collected at the time of event.

A listing for the study eye for subjects for whom images were collected and read by the CRC will be presented.

2.9 Pharmacokinetic endpoints

Not applicable.



[redacted]

2.11 Patient-reported outcomes

Not applicable.

2.12 Biomarkers

Not applicable.

2.13 Other exploratory endpoints

2.13.1 Ophthalmic examination by optical coherence tomography (OCT)

Standardized procedures for the collection of quantitative and qualitative imaging was provided to the clinical sites by the CRC in a separate manual.

Spectral Domain Optical Coherence Tomography

SD-OCT was assessed in the study eye at every study visit and in both eyes at Screening, Visit 14 (Week 52) and Visit 27 (Week 104/EoS) only.

[redacted]

Color fundus photography

Color fundus photography was assessed in both eyes at Screening, Visit 14 (Week 52) and Visit 27 (Week 104/EoS) and in the study eye only at Visit 4 (Week 12).

Data reported (absent/present) are: Fibrosis-central subfield; Fibrosis-inner subfield; Intra-Retinal hemorrhage-inner subfield; Intra-Retinal hemorrhage-central subfield; RPE atrophy-central subfield; RPE atrophy-outer subfield; Sub-Retinal hemorrhage-central subfield; Sub-Retinal hemorrhage-inner subfield

A listing for study eye for all subjects will be presented. Summary statistics will be reported.

As per safety requirements for AMD, shift tables will be reported for geographic atrophy and fibrosis. Both tables will be presented for the study eye. A subject listing will also be presented for geographic atrophy and fibrosis.

Fluorescein Angiography Grade

FA was assessed in both eyes at Screening, Visit 14 (Week 52) and Visit 27 (Week 104/EoS) and in the study eye only at Visit 4 (Week 12).

Data reported for areas of lesion (micometer^2): Area of CNV within a lesion measurement; Area of Lesion associated with CNV; Area of lesion with CNV measurement.
Data reported are listed below:

- CNV location (1 – sub-foveal; 2 – juxta-foveal; 3 – extra-foveal; 4 – cannot grade (unreadable); 5 – not available (missing FA); 6 – not applicable (=absent/no CNV))
- absent/presence of condition: Leakage from CNV; Retinal Angiomatous Proliferation (RAP) Lesions
- type of CNV (1 – classic; 2 – predominantly classic; 3 – minimally classic; 4 – occult-late leakage; 5 – occult fibrovascular PED; 7 – cannot grade (unreadable); 6 – occult-serus PED; 8 - CNV absent; 9 – not available(missing FA))

A listing for study eye for all subjects will be presented. Summary statistics for location, presence of condition, and type of CNV will be reported.

[redacted]

2.14 Interim analysis

There will be one interim analysis after the last subject completes/discontinues his/her Week 52 (primary analysis time point) visit.

The presentation of tables, listings, and figures will include data up to subjects' date of Week 52 visit (inclusive). If a subject missed Week 52 visit, the adverse events and concomitant

medications/procedures started before the date of next scheduled visit after Week 52 will be included. All available data for subjects discontinuing the study prior to Week 52 will be included in the interim analysis.

This interim analysis will be the primary analysis. There will be no hypothesis testing at Week 104. Therefore, no adjustment of the statistical significant level will be made to tests performed at Week 52.

3 Sample size calculation

The primary efficacy variable is change in BCVA from Baseline. The primary analysis time point is Week 52.

As suggested by the US regulatory authority, a non-inferiority margin of 4 letters is considered a clinically acceptable difference of brolucizumab 6 mg dosed every 4 weeks compared to aflibercept 2 mg dosed every 4 weeks in a previously treated population and will be utilized in this study.

In SAVE study (Brown 2013) of ranibizumab (n=87), a standard deviation of 6.4 letters for the change in BCVA from Baseline was observed at Month 3. In ASSESS study (Singh 2015) (n=26), a standard deviation of 9.2 letters was obtained at Month 12. In this study, a standard deviation of 10 letters for the change in BCVA from Baseline to Week 52 in pre-treated subjects is assumed.

To meet US regulatory authority recommendation for safety assessment, data for brolucizumab 6 mg dosed every 4 weeks from at least 300 subjects with 12-month exposure are required. Thus, 450 subjects will be needed with a 2:1 ratio to brolucizumab 6 mg q4 weeks (300 subjects) and aflibercept 2 mg q4 weeks (150 subjects). This sample size is sufficient to demonstrate non-inferiority (margin = 4 letters) of brolucizumab 6 mg q4 weeks versus aflibercept 2 mg q4 weeks with respect to BCVA change from Baseline to Week 52 at a two-sided alpha level of 0.05 with a power of approximately 97% assuming equal efficacy and a common standard deviation of 10 letters. To account for an assumed dropout rate of 12% before Week 52 visit, a total of 513 subjects (342 subjects to the brolucizumab 6 mg q4w arm and 171 to the aflibercept 2 mg q4w arm) will be randomized. The nQuery Advisor 7.0 was used for the above sample size calculations.

Updated Sample size:

According to the current protocol, the target number of subjects to be randomized in RTH arm is 342. The current drop-out rate in the study (both arms) is approximately 0.055/person year (=10/180). Being very conservative (as the study is blinded) and assuming that all dropouts were from RTH arm, the dropout rate in RTH arm is calculated to be 0.083/person year (=10/(180x.67)) due to 2:1 randomization.

To meet US regulatory authority recommendation, at least 300 subjects completing 52 weeks of study with RTH are required. The following table provides probability of having at least 300 RTH subjects completing 52 weeks of study.

Number of subjects randomized to RTH arm	Dropout rate (%)	Probability of observing ≥ 300 RTH subjects completing 52 weeks of study	Note
342	8.0	1.00	
342	8.3	1.00	
342	10.0	0.93	
342	11.0	0.80	
342	12.0	0.60	*Assumed dropout rate in the protocol*
355	8.0	1.00	
355	8.3	1.00	
355	10.0	1.00	
355	11.0	1.00	
355	**12.0**	**0.98**	
355	13.0	0.93	

Based on the above calculation it was decided to increase the current total sample size of the study from 513 to 533, i.e., by 20 more randomized subjects (resulting in approximate 13 additional subjects in RTH). This will provide at least 98% probability of having 300 or more RTH subjects completing 52 weeks of study assuming the maximum dropout rate of 12% in RTH arm as assumed in the protocol.

4 Change to protocol specified analyses

There is no change to protocol specified analysis.

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

5.1.1.1 Adverse event end date imputation

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (31DECYYYY, date of death).
2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (last day of the month, date of death).
3. If AE year is missing or AE is ongoing, the end date will not be imputed.

If the imputed AE end date is less than the existing AE start date, then use AE start date as AE end date.

5.1.1.2 Adverse event start date imputation

The following table explains the notation used in the logic matrix. Please note that completely missing start dates will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Impute AE start date -

If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.

1. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:

   a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

   b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

2. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:

   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).

b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

3. 4. If the AE start date year value is equal to the treatment start date year value:

   a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.

   b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

   c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.2 Concomitant medication date imputation

5.1.2.1 Concomitant medication (CM) 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 (treatment end 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 (treatment end date, last day of the month, date of death).

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.

5.1.2.2 Concomitant medication start date imputation

In order to classify a medication as prior and prior/concomitant, it may be necessary to impute the start date.

Completely missing start dates will be set to one day prior to treatment start date. As a conservative approach, such treatments will be classified as prior and concomitant (and summarized for each output).

Concomitant treatments with partial start dates will have the date or dates imputed.

The following table explains the notation used in the logic matrix:

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.
2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM month is missing, or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior to treatment start date.
    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.1.2.3 Medical history date of diagnosis imputation

Completely missing dates and partially missing end 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

5.1.2.4 Prior therapies date imputation

Not applicable.

5.1.2.5 Post therapies date imputation

Not applicable.

5.1.2.6 Other imputations

5.2 AEs coding/grading

Not applicable.

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

5.4.1 Primary analysis

The ANOVA will be fitted using data from two treatments at a time. RTH258 6mg vs aflibercept 2mg.

Analysis of Variance (ANOVA)

The following ANOVA model will be used for the primary endpoints:

<change from Baseline in BCVA at Week 52>= intercept + treatment + Baseline BCVA category (<= 70, >= 71 letters) + immediate prior treatment (aflibercept or ranibizumab) + time

since first anti-VEGF injection (≤ 36 months, > 36 months) + age category (< 75, >= 75 years) + error.

The following pseudo SAS code will be used to perform the ANOVA analyses:

PROC MIXED DATA=<Dataset> order=Internal;

CLASS <Treatment> <BCVA CAT> <IPT> <TS a-VGEF> <AGE CAT> ;

MODEL <Chg_VA> = <Treatment> <BCVA CAT> <IPT> <TS a-VGEF> <AGE CAT>/SOLUTION

LSMEANS< Treatment> / DIFF CL ALPHA = 0.05 OM;

ODS OUTPUT LSMEANS=outLsm DIFFS=Diffs;

RUN;

Where
<Chg_VA> = primary efficacy endpoint
<BCVA CAT> = baseline BCVA category
<IPT> = immediate prior treatment
<AGE CAT> = age category
<TS a-VGEF> = time since first anti-VEGF injection
<Treatment>= randomized treatment assignment

Mixed Model Repeated Measures (MMRM)

The following MMRM model will be used for the supportive analysis of the primary efficacy variables:
< change from Baseline in BCVA at each schedule post-baseline visit>= intercept + treatment + Baseline BCVA category (<= 70, >= 71 letters) + immediate prior treatment (aflibercept or ranibizumab) + time since first anti-VEGF injection (≤ 36 months, > 36 months) + age category (< 75, >= 75 years) + visit +visit *treatment +error.

The following pseudo SAS code will be used to perform the MMRM analyses:

PROC MIXED DATA=<Dataset> order=Internal;

CLASS USUBJID <Treatment> <BCVA CAT> <IPT> <TS a-VGEF> <AGE CAT><VISIT>;

MODEL <Chg_VA> = <Treatment> <BCVA CAT> <IPT> <TS a-VGEF> <AGE CAT><VISIT>

<VISIT>*<Treatment>

/ solution DDFM=KENWARDROGER ALPHA=0.05;

REPEATED <VISIT>/type=UN subject=USUBJID;

LSMEANS <VISIT>*<Treatment> / DIFF CL ALPHA = 0.05 om;

ODS OUTPUT LSMEANS=outLsm DIFFS=Diffs;

RUN;

Where
<Chg_VA> = primary efficacy endpoint
<BCVA CAT> = baseline BCVA category
<IPT> = immediate prior treatment
<AGE CAT> = age category
<TS a-VGEF> = time since first anti-VEGF injection
<Treatment>= randomized treatment assignment
<VISIT>=category of time point variable

5.4.2 Secondary analysis

Analysis of Variance (ANCOVA)

The following ANCOVA model will be used for the change in CST:

<change from Baseline in CST>= intercept + treatment + immediate prior treatment (aflibercept or ranibizumab) + time since first anti-VEGF injection (≤ 36 months, > 36 months) + age category (< 75, >= 75 years) + baseline CST + error.

The following pseudo SAS code will be used to perform the ANOVA analyses:

PROC MIXED DATA=<Dataset> order=Internal;

CLASS <Treatment> <IPT> <TS a-VGEF> <AGE CAT> ;

MODEL <Chg_CST> = <Treatment> <IPT> <TS a-VGEF> <AGE CAT><Base_CST>/SOLUTION

LSMEANS< Treatment> / DIFF CL ALPHA = 0.05 OM;

ODS OUTPUT LSMEANS=outLsm DIFFS=Diffs;

RUN;

Where
<Chg_VA> = primary efficacy endpoint
<BCVA CAT> = baseline BCVA category
<IPT> = immediate prior treatment
<AGE CAT> = age category
<TS a-VGEF> = time since first anti-VEGF injection
<Treatment>= randomized treatment assignment

For marginal standardization method, the categorical variable will be analyzed using the logistic regression model adjusted for treatment and age category, using the FAS.

The SAS Proc LOGISTIC will be used.

Note:

- For the above analyses, the data structure is one record per patient and visit.The least square mean estimates obtained from the above model are for the log-odds ratios.

- The estimated difference in proportions and the corresponding 95% confidence intervals will be obtained by applying the bootstrap method. The pseudo SAS code to derive the treatment difference and 95% CI from the least square mean output of the fitted model will be provided in the programming specification document.

For the analyses of time to event variabes,

ODS LISTING CLOSE;

PROC LIFETEST DATA = <xxx> OUTSURV = <xxx> ;

TIME time*censor(0);

ODS OUTPUT PRODUCTLIMITESTIMATES = res;

ODS OUTPUT HOMTESTS=pvalue;

ODS OUTPUT QUARTILES=med;

RUN;

ODS LISTING;

5.5 Rule of exclusion criteria of analysis sets

Table 5-1 includes the important protocol deviations which lead to exclusion of subjects from one or more analysis sets.

Table 5–1 Important protocol deviations leading to exclusion from analysis

Deviation ID (Code)	Description of the Deviation ID	Exclusion in Analysis	Comment
INCL01	Signed informed consent was not obtained prior to participation in the study	Exclude from all analysis	
INCL02	Subjects was not 50 years of age or older at Screening	Include in all analysis	
INCL03A	Study eye: Absence of active nAMD in appropriate location confirmed by CRC at screening	Exclude from PPS analysis	
INCL06	Study eye: BCVA score outside limits defined in protocol, at screening or baseline	Exclude from PPS analysis (conditionally on comment)	Yes/No. Note: 4 letters is considered natural

			within subject variability.
INCL07	Study eye: First anti-VEGF injection in the study eye less than 9 months prior to Screening or less than 7 injections within last 9 months prior to Screening	Exclude from PPS analysis (conditionally on comment)	Yes/No. Note: exclude if less than 5 injections.
EXCL01	Study eye: Subject had active intra-ocular or peri-ocular infection or active intra-ocular inflammation in either eye at Screening and Baseline	Exclude from PPS analysis (conditionally on comment)	PPS=NO, if in the study Eye PPS=YES, if in the fellow Eye Note: EXCL01 code will be assigned based on medical assessment
EXCL05A	Study eye: Presence of fibrosis, retinal atrophy or sub-retinal blood exclusionary criteria confirmed by CRC at screening	Exclude from PPS analysis	
EXCL09K	Study eye: History of evidence of concomitant ocular condition in the study eye with impact on efficacy and/or safety	Exclude from PPS analysis	
EXCL09L	Study eye: History of ocular procedure or therapy in the eye with impact on efficacy and/or safety	Exclude from PPS analysis	
EXCL09M	Study eye: prohibited ocular medication in the study eye	Exclude from PPS analysis (conditionally on comment)	If at screening then PPS=NO PPS=YES, otherwise
EXCL10A	Study eye: History of prohibited systemic medication	Include in all analysis	

	without impact on efficacy/safety		
EXCL11A	Study eye: History of systemic condition with impact on efficacy/safety	Include in all analysis	
EXCL14A	Study eye: History of prohibited systemic medication with impact on efficacy/safety	Exclude from PPS analysis (conditionally on comment)	Note: If PD has been confirmed by medical team then exclude from PPS.
EXCL17	Study eye: Subject was pregnant or nursing, or a woman of childbearing potential not using highly effective method of contraception while on Tx and 3mos after last dose.	Include in all analysis	
TRT02A	Study eye: Missed active treatment not due to any safety event	Exclude from PPS analysis (conditionally on comment)	PPS=NO, if 2 or more consecutive missed injections prior to Week 52 PPS=YES, if otherwise
TRT05	Study eye: Incorrect assignment of study treatment group	Exclude from PPS analysis (conditionally on comment)	PPS=NO, if prior to Week 44 assessment
TRT06A	Study eye: Administered IP that underwent a temperature excursion.	Include in all analysis	
TRT07	Missed active treatment due to COVID-19	Exclude from PPS analysis (conditionally on comment)	PPS=NO, if 2 or more consecutive missed injections prior to Week 52 PPS=YES, if otherwise

OTHER04	Masking process not followed per protocol with impact on data integrity	Include in all analysis	
OTHER06	BCVA not performed correctly with relevant potential to confound the key efficacy assessments	Exclude from PPS analysis (conditionally on comment)	PPS=YES, if there is a valid BCVA assessment **on study treatment** at baseline, and one valid BCVA assessment out of Weeks 44, 48 and 52 **(Analysis window, globally applicable, excluding unscheduled assessment)** PPS=NO otherwise
OTHER07	Any protocol deviation with impact on subjects safety and/or efficacy assessment	Exclude from PPS analysis (conditionally on comment)	PPS=YES, if there is a valid BCVA assessment **on study treatment** at baseline, and one valid BCVA assessment out of Weeks 44, 48 and 52. PPS=NO otherwise
OTHER08	Missed visit due to COVID-19	Exclude from PPS analysis (conditionally on comment)	PPS=YES, if there is a valid BCVA assessment **on study treatment** at baseline, and one valid BCVA assessment out of Weeks 44, 48 and 52. PPS=NO otherwise
OTHER09	Masking process not followed per protocol due to COVID-19	Exclude from PPS analysis (conditionally on comment)	PPS=YES, if there is a valid BCVA assessment **on study treatment** at baseline, and one valid BCVA assessment out of Weeks 44, 48 and 52. PPS=NO otherwise

OTHER10	Study treatment discontinued due to COVID-19	Exclude from PPS analysis (conditionally on comment)	PPS=YES, if there is a valid BCVA assessment **on study treatment** at baseline, and one valid BCVA assessment out of Weeks 44, 48 and 52. PPS=NO otherwise
OTHER11	BCVA not performed correctly due to COVID-19	Exclude from PPS analysis (conditionally on comment)	PPS=YES, if there is a valid BCVA assessment **on study treatment** at baseline, and one valid BCVA assessment out of Weeks 44, 48 and 52. PPS=NO otherwise
OTHER12	Impact on subjects safety and/or efficacy assessment due to COVID-19	Exclude from PPS analysis (conditionally on comment)	PPS=YES, if there is a valid BCVA assessment **on study treatment** at baseline, and one valid BCVA assessment out of Weeks 44, 48 and 52. PPS=NO otherwise
OTHER13	Accidental unmasking happened to study team due to query wordings in EDC	Include in all analysis	
COMD01A	Prohibited ocular medication and/or procedure in the study eye	Exclude from PPS analysis (conditionally on comment)	PPS=YES, if there is a valid BCVA assessment **on study treatment** at baseline, and one valid BCVA assessment out of Weeks 44, 48 and 52. PPS=NO otherwise Note: exclusion of all subsequent visits COMD01 code will be assigned if any of the following treatments reported: • aflibercept,

			• bevacizumab, • ranibizumab (and biosimilar), • pegaptanib, • intra- or periocular corticosteroids • (unless used for treating an ocular • adverse event) • laser treatment for nAMD • any other investigational drug (based on medical review)
COMD04A	Prohibited ocular medication and/or procedure in the fellow eye	Include in all analysis	
COMD06A	Prohibited systemic medication	Exclude from PP analysis (conditionally on comment)	PPS=YES, if there is a valid BCVA assessment **on study treatment** at baseline, and one valid BCVA assessment out of Weeks 44, 48 and 52. PPS=NO otherwise
WITH01	Patient Withdrew consent. However dose was administered.	Exclude from PP analysis (conditionally on comment)	PPS=YES, if there is a valid BCVA assessment **on study treatment** at baseline, and one valid BCVA assessment out of Weeks 44, 48 and 52. PPS=NO otherwise
WITH02	Patient met one or more of the Discontinuation of Study Drug criteria however, study drug was not discontinued	Exclude from PP analysis (conditionally on comment)	PPS=YES, if there is a valid BCVA assessment **on study treatment** at baseline, and one valid BCVA assessment out of Weeks 44, 48 and 52. PPS=NO otherwise

TRT06A *	Administered IP that underwent a temperature excursion	Include in all analysis	
TRT05 *	Incorrect assignment of study treatment group	Exclude from PPS analysis (conditionally on comment)	PPS=NO, if prior to Week 44 assessment
* masked PD during the study conduct			

Table 5-2 lists the non-protocol deviations (analysis restrictions) that may lead to exclusion from per-protocol analysis. ARs address limitations in the evaluability which result from missing or confounded data with underlying background not qualifying as a PD (e.g. early study terminations, early treatment discontinuations, missing visits / missed treatments).

Rules of determination of ARs by programming will be specified in the programming Data Specifications (PDS) documentation.

Table 5-2 Non-protocol deviations (analysis restrictions)

AR ID	Description of AR	Category of reason	Exclusion in Analyses
AR_EST_01	Early study treatment discontinuationdue to any reason other than lack of efficacy/safety before or/at Week 52	0	PPS=Yes, if there is a valid BCVA assessment **on study treatment** at baseline, and one valid BCVA assessment out of Weeks 44, 48 and 52. PPS=No otherwise
AR_EST_02	Early study treatment discontinuation due to lack of efficacy/safety before or at Week 52	1,2	Include in all analysis

Subject evaluability is based on two components:

1. Exclusion from an analysis set
2. Censoring of specific data points from an analysis (see Section 5.6).

The consequence of an AR on the evaluability depends on the underlying reason, while three different categories of reason are considered:

1. Lack of efficacy of the study treatment (=1)
2. Lack of safety / tolerability of the study treatment (=2)
3. Other (=0)

Remark: Based on the concept of PD's, their underlying reason will always be '0'.

As a general rule, ARs with a reason of 1 or 2 do not lead to an exclusion from any analysis set, as a potential link between exclusion reason and treatment would constitute a source for systematic bias.

Table 5-3 describes subject classification with regards to analysis sets:

Table 5-3 Patient Classification

Analysis Set	PD ID that may cause subjects to be excluded	Non-PD (AR) ID that cause subjects to be excluded
RAS	INCL01	N/A
FAS	INCL01	N/A
SAF	INCL01	N/A
PPS	INCL01 INCL03A INCL06* INCL07* EXCL01* EXCL5A EXCL09K EXCL09L EXCL09M* EXCL14A* TRT02A* TRT05* TRT07* OTHER06* OTHER07* OTHER08* OTHER09* OTHER10* OTHER11* OTHER12* COMD01A* COMD06A* WITH02*	AR_EST_01 AR_EST_02

***See Table 5-1 comments for conditions of exclusion.**

5.6 Restricted Medications

Table 5–4 Prohibited Medications

Prohibited medication & procedure	Examples list (may not be all inclusive)	Specification	Identification method	PD code	PD term
Study eye					
Anti-VEGF treatments in **study eye**	Ranibizumab (Lucentis) Brolucizumab (Beovu) Aflibercept (Eylea) Pegaptanib (Macugen	Any time in study eye	Programmatically, by administration route (intravitreal)	COMD01A	Prohibited ocular medication and/or procedure in the study eye

	Bevacizumab (Avastin)				
Intra- or periocular corticosteroids in the study eye	Triamcinolone Dexamethasone	Any time during the study (except if for treatment of AE)	Assigned PD		
Fellow eye					
Investigational treatment (Bevacizumab (Avastin) is allowed)		Any time during the study	Assigned PD	COMD04A	Prohibited ocular medication and/or procedure in the fellow eye
Anti-VEGF	Brolucizumab (Beovu)	Any time during the study	Programmatically, by administration route (intravitreal)		
Systemic medications					
Chronic use (≥ 30 consecutive day) of systemic corticosteroids	Dexamethasone Difluprednate Fluorometholone Hydrocortisone Prednisolone acetate Cyclosporine	Any time during the study Low stable dose of systemic corticosteroids, inhaled, nasal, or dermal steroids are allowed	Assigned PD	COMD06A	Prohibited systemic medication
Systemic Anti-VEGF therapy /antineoplastic	Bevacizumab (Avastin)	Any time during the study	Programmatically, (as systemic administration – intravenous))		
Investigational drug, or biologic or devise		Any time during the study	Assigned PD		
Medications known to be toxic to the lens, retina or optic nerve (to be excluded if	Ethambutol, chloroquine/ hydroxychloroquine, deferoxamine, phenothiazines tamoxifen	Any time during the study (except temporary use for COVID-19 treatment)	Assigned PD	COMD06A	

started after 01-Jul-2020)					

Medication (brand name)	ATC code for **ocular** (IVT) administration	ATC code for **systemic** (intravenous) administration
Ranibizumab (Lucentis)	L01XC07	Not available
Brolucizumab (Beovu)	S01LA06	Not available
Aflibercept (Eylea)	S01LA05	L01XX44
Pegaptanib (Macugen)	S01LA03	Not available
Bevacizumab (Avastin) [Prohibited in study eye - Permitted in fellow eye]	Not available for AMD indication, but the code L01XCO7 would be used	L01XCO7

6 Reference

Heier J, Brown D, Korobelnik J, et al. (2012) Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology; 119:2537-48.

Singh RP, Srivastava SK, Ehlers JP, et al. (2015) A single-arm, investigator-initiated study of the efficacy, safety, and tolerability of intravitreal aflibercept injections in subjects with exudative age-related macular degeneration previously treated with ranibizumab or bevacizumab (ASSESS study): 12-month analysis. Clin Ophthalmol; 9:1759-66.