NOVARTIS

Novartis Research and Development

RTH258/Brolucizumab

CRTH258A2303E1 / NCT04597632

A 56-week phase IIIb/IV, open-label, one-arm extension study to assess the efficacy and safety of brolucizumab 6 mg in a Treat-to-Control regimen with maximum treatment intervals up to 20 weeks for the treatment of patients with neovascular age-related macular degeneration who have completed the CRTH258A2303 (TALON) study

Statistical Analysis Plan (SAP)

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17-May-2021	Prior to DB lock	Addition of covid-19 impact analyses Added are paragraphs describing the analyses of AEs starting in the Core, prior medical procedures, etc	Amendment 1 Amendment 2	Section 2.2.1 Section 2.3.1 Section 2.4.2 Section 2.5.4 Section 2.7.1 Section 2.8
8-Mar-2022	Prior to DB lock	Addition of analyses addressing the urgent safety measures Clarification on AEs leading to treatment discontinuation Extended sample size analyses Clarified “extension baseline” when “baseline” is stated and meant the extension baseline, as in the protocol Removed duplicate sentences and re-arranged paragraphs Medical history description moved from Sec 2.4.2 to 2.3 Amended protocol 02 as a reference BCVA categories to be the same as in the Core SAP Added detail about missing data handling Added IRF/SRF and CSFT summaries at the last treatment visits and 4 weeks after for discontinued participants Added detail on the laboratory data analyses		Section 2.2.1 Section 2.5.4 Section 2.6.1 Section 2.7.1 Section 2.7.1 Section 3 Section 1.1 Section 1.2 Section 2.2.1 Section 2.3 Section 2.4.1 Section 2.4.2 Section 2.5 Section 2.6.1 Section 2.7.1 Section 2.7.4 Section 2.12 Section 2.7.1 Section 2.3 Section 2.4.2 Section 1 Section 2.2.1 Section 2.5.3 Section 2.6.3 Section 2.6.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
		The sentence revised to be the same as in the Core SAP		Section 2.7.1 Section 2
28-Mar-2023	Prior to DB lock	Adjusted the wording and formatting of the SAP	Amendment 3	
		Specified the analysis responsibilities		Section 2
		Revised the name of Enrollment Set and the definition of PPS		Section 2.2
		Removed the subgroup analysis		Section 2.2.1 Section 2.3 Section 2.5.4 Section 2.7.1
		Removed the duplications		Section 2.4.1
		Updated the statistical model for ANCOVA and MMRM		Section 2.5.2 Section 2.5.4 Section 2.6.2
		Updated the primary, supportive and sensitivity estimands		Section 2.5.3 Section 2.5.4
		Updated the analysis part for secondary endpoints		Section 2.6.1
		Added the defintion of TEAE and contend for CTSD		Section 2.7.1
		Added the loss in BCVA		Section 2.7.3
		Remove section for laboratory data		Section 2.7.4
		Added the PD list and AR that cause participants to be excluded from PPS		Section 5.5

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List of abbreviations

Abbreviation	Definition
AE(s)	Adverse Event(s)
AESI	Adverse Event of Special Interest
ANOVA	Analysis of Variance
AR	Analysis Restrictions
ATC	Anatomical Therapeutic Chemical
BCVA	Best-Corrected Visual Acuity
CI(s)	Confidence Interval(s)
CFP	Color Fundus Photography
CM	Concomitant Medication
CNV	Choroidal Neovascularization
COVID-19	Coronavirus disease 2019
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study Report
CRS	Case Retrieval Sheet
CSFT	Central Subfield Thickness
DA	Disease Activity
CSR	Clinical Study Report
DAA	Disease Activity Assessment
eCRF	Electronic CRF
EOS	End of Study
EOT	End of Treatment
FA	Fluorescein Angiography
FAS	Full Analysis Set
ICF	Inform Consent Form
LLN	Lower Limit of Normal
IRF	Intraretinal Fluid
IOP	Intraocular Pressure
LOCF	Last Observation Carried Forward
LSM	Least-Squares Mean
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed Model for Repeated Measures
nAMD	neovascular Age-related Macular Degeneration
OCT	Optical Coherence Tomography
PD(s)	Protocol Deviation(s)
PDS	Programming Datasets Specifications
PPS	Per-Protocol Set
PT	Preferred Term
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event

Abbreviation	Definition
SAP	Statistical Analysis Plan
SD-OCT	Spectral Domain Optical Coherence Tomography
SE	Standard Error
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SRF	Subretinal Fluid
TFL	Tables, Figures and Listings
TtC	Treat-to-Control
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

1 Introduction

This document describes the detailed statistical methodology to be used for the Clinical Study Report (CSR) of the TALON-extension study CRTH258A2303E1; a 56-week, phase IIIb/IV, open-label, one-arm extension study to assess the efficacy and safety of brolucizumab 6 mg in a Treat-to-Control (TtC) regimen with maximum treatment intervals up to 20 weeks for the treatment of participants with neovascular age-related macular degeneration (nAMD) who have completed the CRTH258A2303 (TALON-core) study.

The content of this Statistical Analysis Plan (SAP) is based on amended protocol version 02. All decisions regarding the final analysis, as defined in this SAP document, will be made prior to final database lock and unblinding of the study data.

CSR deliverables (shells for tables, figures, listings [TFLs]) and further programming specifications will be described in the TFL shells and Programming Datasets Specifications (PDS), respectively.

1.1 Study design

The study is a 56-week open-label, multi-center, one-arm extension study in participants with nAMD who have completed the TALON core study.

Approximately 250 participants from the core study (CRTH258A2303, TALON) will enter this extension study. The primary analyses will be conducted when all ongoing participants have completed their Week 56 visit and after the database lock.

1.2 Study objectives and endpoints

The study objectives and corresponding endpoints as specified in the protocol are provided in Table 1-1.

Table 1-1 Study objectives and endpoints

Objectives	Endpoints	Analysis
Primary objectives	**Endpoints for primary objectives**	**Analysis**
• To evaluate the extended durability of brolucizumab in a TtC regimen with respect to the duration of treatment intervals at Week 56	• Duration of the last interval with no DA up to Week 56	Section 2.5
• To evaluate the functional outcomes of brolucizumab in a TtC regimen with respect to average change in BCVA at Week 52 and Week 56	• Change in BCVA from extension baseline at Week 52 and Week 56	
Secondary objectives	**Endpoints for secondary objectives**	**Analysis**
• To evaluate the anatomical outcomes of brolucizumab in all patients and per randomized arm in the core study	• Change in CSFT from extension baseline to Week 52 and Week 56 Number of visits with presence of IRF and/or SRF,	Section 2.6

Objectives	Endpoints	Analysis
	and sub-RPE fluid in the central subfield, as assessed by SD-OCT at Week 52 and Week 56	
• To assess the durability of brolucizumab in all patients and/or per randomized arm in the core study	• Duration of the last interval with no DA up to Week 56 Duration of the maximal intervals with no DA up to Week 56 Change of the duration of last interval with no DA between extension baseline and Week 56	
• To assess the functional outcomes of brolucizumab per randomized arm in the core study	• Change in BCVA from extension baseline to Week 52 and Week 56	
• To assess the safety of brolucizumab	• Occurrence of Ocular and Non-ocular AEs up to Week 56	Section 2.7

[redacted]

2 Statistical methods

All analyses described in the SAP will be performed by Novartis. Any additional (or other) data analysis carried out independently by the investigators should be submitted to Novartis before publication or presentation.

2.1 Data analysis general information

Categorical data will be presented as frequencies and percentages. For continuous data, n, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented (when applicable).

2.1.1 General definitions

All the definitions, e.g. baseline, on-treatment period, are referring to the current extension study unless otherwise stated, e.g. baseline of the core study.

Study treatment is defined as brolucizumab 6 mg/0.05 mL.

Date of first administration of study treatment is defined as the first date when a non-zero dose of study treatment is administered and recorded on the case report form (CRF) dose administration page. The date of first administration of study treatment will also be referred to as start of study treatment.

Date of last administration of study treatment is defined as the last date when a non-zero dose of study treatment is administered and recorded on the CRF dose administration page. The last administration of study treatment will also be referred as end of treatment (EOT).

Study day will be calculated as:

- The date of the event (visit date, onset date of an event, assessment date etc.) – treatment start date + 1, if event is on or after the treatment start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) – treatment start date, if event precedes the treatment start date.

Baseline/Day 1 is the end of study (EOS)/Week 64 of the core study.

On-treatment period is defined from Day 1 of the study to 30 days after the last administration of study treatment (i.e. EOT) or end of study (EOS), whichever is the latest.

Treatment interval is defined as the time period from one injection until the next injection. In this study, treatment intervals of q4w, q8w, q12w, q16w and q20w, meaning that there are 4, 8, 12, 16 and 20 weeks between 2 injections, are of special interest. The last (treatment) interval at Week X is referred to the last complete interval where injections at both ends of the interval have occurred on or before Week X. The last interval with/without disease activity is referred to the last interval with/without disease activity as observed at the end of the interval.

The first treatment is defined by the treatment interval of the core study. For example, a patient who started a 16-weeks interval at Week 56 of the core study will have the first treatment 8 weeks after the start of the extension study (i.e. 8 weeks after Week 64).

Participants will be assessed for eligibility based on inclusion and exclusion criteria for the extension study at the baseline visit.

The study day will be displayed in data listings. All data from scheduled and unscheduled visits will be analyzed based on “Week XX” recorded in the CRF (except for baseline), unless otherwise stated.

2.2 Analysis sets

The **Enrollment Set** includes all participants who signed the informed consent form (ICF) and are assigned participant numbers. This analysis set will be used to summarize the disposition of participants, pre-treatment adverse events (AEs) and counts of AEs during the on-treatment period.

The Full Analysis Set (FAS) comprises of all participants who received at least one dose of study treatment in the extension study. This analysis set will serve as the primary analysis set for all efficacy and safety analyses.

The Per-Protocol Set (PPS) is a subset of participants in the FAS with major protocol deviation (with impact). Patients with important PDs but without impact will be reported as PD and will be included in PPS.

The list of protocol deviation criteria will be provided in the edit check specification document. Please refer to Table 5-1 for more details.

2.2.1 Subgroup of interest

Primary endpoint analysis for BCVA will be conducted using the following baseline BCVA and age categories:

- Baseline BCVA categories: < 55, 55-< 73, ≥ 73 letters read,
- Age categories: < 75, ≥ 75 years old.

2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other extension study baseline data including disease characteristics will be summarized by appropriate descriptive statistics for all analyses sets. A listing will also be provided.

A baseline (of the extension study) disease characteristic table will be provided by treatment groups of the core study and overall, including:

- Primary diagnosis of nAMD, time since diagnosis of nAMD (days), whether nAMD is unilateral or bilateral and intraocular pressure (IOP).
- BCVA (as a continuous variable and using categories (< 55, 55-< 73, ≥ 73 letters read)),
- OCT angiography parameters – if collected.
- SD-OCT parameters (IRF, SRF, sub-RPE, CSFT (as a continuous variable and using categories (< 400, ≥ 400 µm)) and lesion type).
- CFP parameters (intra-retinal hemorrhage – central subfield, sub-retinal hemorrhage – central subfield, RPE atrophy – outer subfield, RPE atrophy – central subfield, fibrosis – inner subfield, fibrosis – central subfield).
- FA parameters (type of CNV, area of CNV within the lesion, CNV location, leakage from CNV).

Relevant medical histories and current medical conditions at baseline of the extension study will be summarized separately by system organ class and preferred term for the FAS.

Medical history/current medical conditions will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of the analyses. The MedDRA version used for reporting will be specified in the clinical study report (CSR) and as a footnote in the applicable tables/listings.

Medical histories which started before the core study and are ongoing on Day 1 of the extension study will be recorded on the Medical History eCRF. Data collected for the Medical History

eCRF for the extension study will be presented by the treatment arm in the core study and overall. Columns will be included to identify if the event started before the core study, during the core study, or during the extension study; and if the event is ongoing or ended during the Extension study.

2.3.1 Patient disposition

Patient disposition for all participants will be summarized based on the Enrollment Set. A listing will also be provided.

The number (%) of participants in the FAS and PPS will be presented based on the Enrollment Set. Participants excluded from the FAS and PPS including the corresponding reasons will be presented in a listing.

A listing of all important protocol deviations with their respective deviation/restriction categories will be provided. A summary table for PDs will also be provided (if appropriate). The number and percentage of participants with important PDs will be presented by deviation/restriction category. Due to the COVID-19 pandemic, a higher number of PDs are expected. To evaluate the PDs occurring due to the COVID-19 pandemic, the number and percentage of participants with PDs occurring due to the COVID-19 outbreak will also be provided by deviation category. A listing of PDs will be provided by participant, including the relationship to COVID-19, and the information if the PD led to exclusion of the participant from an analysis set.

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

2.4.1 Study treatment / compliance

The FAS will be used for the analyses below.

[redacted]

2.4.2 Prior, concomitant and post therapies

Concomitant medications and significant non-drug therapies prior to and after start of study treatments will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system based on Enrollment Set.

Medications taken at least once during the extension study and medications started on the end of study visit date for the core study/extension study baseline visit date will be recorded on the Concomitant Medications eCRF.

Prior medications (ocular and non-ocular) will be summarized using number and percentage of patients by ATC class and PT according to the World Health Organization (WHO) drug reference list directory. Prior ocular medications will be summarized overall and separately for

the study and fellow eye; and by the treatment arm in the core study. Prior medications are those that have a start date prior to the date of the first administration of study treatment in this extension study.

A concomitant medication is defined as any medication taken at least once after the first administration of study treatment in this extension study. Concomitant medications will be summarized.

Procedures occurring during the extension study and procedures occurring on the end of study visit date for the core study/extension study baseline visit date will be recorded on the Procedures eCRF.

Prior surgical and medical procedures are those that have a start date prior to the date of the first injection of study treatment in this extension study.

2.5 Analysis of the primary objective

The primary objectives of the study are:

- To evaluate the extended durability of brolucizumab in a TtC regimen with respect to the duration of treatment intervals up to Week 56.
- To evaluate the functional outcomes of brolucizumab in a TtC regimen with respect to average change in BCVA at Week 52 and Week 56, i.e., change from the extension study baseline to the average of Week 52 and Week 56.

2.5.1 Primary endpoint

The primary endpoints of the study are:

- Duration of the last interval with no disease activity up to Week 56.
- Average change in BCVA from baseline of the extension study at Week 52 and Week 56.

Primary estimands along with the sensitivity estimands are shown in Table 2-1.

2.5.2 Statistical hypothesis, model, and method of analysis

The average change in BCVA from baseline of the extension study at Week 52 and Week 56 will be estimated by an analysis of variance (ANOVA) with baseline age categories, baseline BCVA categories and treatment arm in the core study included as fixed effects. The estimate of BCVA change will be accompanied by the 95% CI.

For the analysis of durability, the first step is to identify the last (treatment) interval with respect to Week 56 for each participant, i.e. the last interval for which injections have occurred at both ends of this interval before/at Week 56. If there is disease activity at the end of the last interval, then the last interval will be shortened by 4 weeks, down to a minimum of q4w. Subjects who do not receive any injection (or only one injection) of study drug in the extension study will be excluded from this analysis. In case of any treatment interruption or permanent study treatment discontinuation, the imputation techniques as per the estimand framework in Section 2.5.3 will be considered. Then, the proportion of participants with last interval of q4w, q8w, q12w, q16w, and q20w will be specified. These proportions will be referred as the distribution of the last interval.

The distribution of the last interval with no disease activity up to Week 56 will be described based on counts and proportions of participants at 4-week, 8-week, 12-week, 16-week, and 20-week intervals. These proportions will be accompanied by 95% CIs. The counts and proportions will be accompanied by 2-sided 95% CIs inferred based on binomial distribution for each endpoint and 2-sided 95% simultaneous CIs inferred using the Goodman method (Goodman 1965). The Goodman method is used for obtaining simultaneous CIs for the parameters of a multinominal distribution, for example for a multinomial endpoint (4-week interval, 8-week interval, 12-week interval, 16-week interval, and 20-week interval).

2.5.3 Handling of missing values/censoring/discontinuations

The imputation of missing data will be handled by defining the estimand framework. The primary estimands is described by the following attributes:

1. Population: participants who have completed the CRTH258A2303 study (TALON) irrespective of the study treatment received in the core study.
2. The co-primary variable 1 is change in BCVA from extension baseline at Week 52 and Week 56, i.e. the average change in BCVA from extension baseline to Week 52 and Week 56. The co-primary variable 2 is the duration of the last interval with no disease activity up to Week 56, i.e. the proportion of participants in q4w, q8w, q12w, q16w and q20w intervals (interval distribution) at last interval with no disease activity up to Week 56 (subjects who will be assigned to a 4-week interval will be analyzed as such, but discontinued from further study treatment).
3. Treatment of interest: brolucizumab 6 mg will be taken for the entire study duration.
4. Handling of remaining intercurrent events:
    - Study treatment discontinuation: For the co-primary endpoint of change in BCVA, a hypothetical treatment strategy will be applied to estimate the treatment effect under the hypothetical assumption that the patient would not start an alternative anti-VEGF treatment (i.e. standard of care therapy) on the study eye. For the co-primary endpoint of duration of treatment interval, a ‘while on treatment strategy’ will be applied as disease stability assessment will not be performed after the patient discontinued treatment.
    - Study treatment interruption: For both the co-primary endpoints, a treatment policy strategy will be applied.

The summary measure for the co-primary variable 1 is the interval distribution, and for the co-primary variable 2 is the least square means.

The primary estimands and other supportive estimands of interest are described in Table 2-1 below, together with their key attributes.

For all participants, the last potential study treatment will be at the Week 52 visit. Participants who will receive a study treatment at an inspection visit may have a study visit at Week 54. For those participants, the Week 54 visit will take place in lieu of the visit at Week 52. Hence throughout this document, analyses based on Week 52 BCVA and other efficacy data are performed if Week 52 data are available. If Week 52 BCVA and other efficacy data are not available, Week 54 BCVA and other efficacy data will be used instead of Week 52. Otherwise, LOCF will be used to impute missing BCVA as per the estimand framework.

Table 2-1 Primary and sensitivity estimands

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Primary estimand 1 (Duration of last interval with no disease activity)	Duration of the last interval with no disease activity, i.e., distribution of the last interval with no disease activity up to Week 56, i.e., proportion of participants in last interval with no disease activity that is 4/8/12/16/20-weeks intervals	FAS *Last interval with no disease activity up to Week 56.	'While on treatment strategy' will be applied as disease stability assessment will not be performed after the patient discontinued treatment.	Treatment policy strategy will be applied, i.e., include data collected after treatment interruption	Two-sided 95% CI of proportions. If there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks
Primary estimand 2 (change in BCVA)	Change in BCVA from baseline of the extension study at Week 52 and Week 56, i.e., the average difference in BCVA between baseline of the extension study and the average of Week 52 and Week 56	FAS All data collected until the participant discontinued the study treatment and started alternative treatment(s) will be included.	The hypothetical treatment strategy will be applied , i.e, exclude data collected after study treatment discontinuation, treat them as missing and impute with LOCF	Treatment policy strategy will be applied, i.e., include data collected after treatment interruption	Two-sided 95% CI obtained from ANOVA with baseline age categories, baseline BCVA categories and treatment arm in the core study included as fixed effects

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Sensitivity estimand 1.2 (Duration of last interval with no disease activity, and excluding participants with important protocol deviations as per PPS)	Duration of the last interval with no disease activity, i.e., distribution of the last interval with no disease activity up to Week 56, i.e., proportion of participants in last interval with no disease activity that is 4/8/12/16/20-weeks intervals.	PPS** *Last interval with no disease activity up to Week 56.	'While on treatment strategy' will be applied as disease stability assessment will not be performed after the patient discontinued treatment.	Treatment policy strategy will be applied, i.e., include data collected after treatment interruption	Two-sided 95% CI of proportions. If there was disease activity, the last interval will be shortened by 4 weeks, down to a minimum of 4 weeks
Sensitivity estimand 2.2 (change in BCVA, and excluding participants with important protocol deviations as per PPS)	Change in BCVA from Baseline of the extension study at Week 52 and Week 56, i.e., the average difference in BCVA between Baseline of the extension study and the average of Week 52 and Week 56	PPS All data collected until the participant discontinued the study treatment and started alternative treatment(s) will be included.	The hypothetical treatment strategy will be applied, i.e, exclude data collected after study treatment discontinuation, treat them as missing and impute with LOCF	Treatment policy strategy will be applied, i.e., include data collected after treatment interruption	Two-sided 95% CI obtained from ACOVA with baseline age categories, baseline BCVA categories and treatment arm in the core study included as fixed effects

Estimand	Estimand definition	Analysis set, data included in the analyses	Use of data after intercurrent event (missing data imputation techniques)		Statistical methods
			Discontinuation of study treatments	Treatment interruption	
Sensitivity estimand 2.3 (change in BCVA)	Change in BCVA from Baseline of the extension study at Week 52 and Week 56, i.e., the average difference in BCVA between Baseline of the extension study and the average of Week 52 and Week 56	FAS All data collected until the participant discontinued the study treatment and started alternative treatment(s) will be included.	Analyze on observed data only	Analyze on observed data only	Two-sided 95% CI obtained from MMRM with age categories at the baseline, BCVA categories at the baseline, treatment arm in the core study, and assessment visit as the fixed effect and participant as a random effect

* If the duration of the last interval falls within the following ranges of [q4w, q8w) or [q8w, q12w), [q12w, q16w), [q16w, q20w) or ≥ q20w then the floor value of these ranges i.e., q4w, q8w, q12w, q16w, q20w, respectively, will be used for imputation.

** Participants who take prohibited concomitant medication are already excluded from PPS as taking prohibited medication is considered a deviation with impact.

2.5.4 Sensitivity analyses

Sensitivity analyses for the two co-primary endpoints will be performed to examine robustness with respect to PDs based on the PPS.

To evaluate robustness of the analyses for the co-primary endpoint (change in BCVA from extension baseline at Week 52 and Week 56) that were based on the LOCF method, sensitivity analyses will be performed on the observed data in the FAS and MMRM. The MMRM model will include the change in BCVA as the dependent variable, age categories at baseline, BCVA categories at baseline, treatment arm in the core study, and assessment visit as the fixed effects and participant as a random effect.

2.6 Analysis of secondary objectives

The FAS will be used to analyze durability, functional, tolerability and anatomical outcomes.

2.6.1 Secondary endpoints

The following secondary endpoints evaluate the anatomical outcomes of brolucizumab in all participants and per randomized arm in the core study:

- Summary statistics of average change in CSFT from baseline of the extension study at Week 52 and Week 56 will be provided. In addition, equivalent summaries will be provided for participants who discontinued the study treatment early at the date of the last treatment and 4 weeks after.
- Summary statistics of average change in CSFT from baseline of the core study to Week 52 and Week 56 will be provided.
- Number (%) of patients with presence of IRF and/or SRF and sub-RPE fluid in the central subfield, as assessed by SD-OCT at Week 52 and Week 56 and by the number of visits will be provided. In addition, equivalent summaries will be provided for participants who discontinued the study treatment early at the date of the last treatment and 4 weeks after.

The following secondary endpoints evaluate the durability of brolucizumab in all participants and per randomized arm in the core study:

- Distribution of the duration of the last interval with no disease activity up to Week 56 will be provided.
- Distribution of the duration of the maximal intervals with no disease activity up to Week 56 will be provided.
- Distribution of the change of the duration of last interval with no disease activity between baseline of the extension study and Week 56 will be provided.

The following secondary endpoints evaluate the functional outcomes of brolucizumab per randomized arm in the core study:

- Summary statistics of the average change in BCVA from baseline of the extension study to Week 52 and Week 56 will be provided.

The following secondary endpoints evaluate the functional outcomes of brolucizumab in all participants and per randomized arm in the core study:

- Summary statistics of the change in BCVA from the baseline of the core study by visit will be provided. Boxplots with a trend line and the line plot of LSM (+/-SE) by visit will also be graphed.
- Summary statistics for the average change in BCVA from the baseline of the core study to Week 52 and Week 56 will be provided.

2.6.2 Statistical hypothesis, model, and method of analysis

Counts and proportions for the endpoints describing durability, tolerability, and anatomical outcomes (i.e., number of visits with presence of IRF and/or SRF) will be accompanied by 2-sided 95% CI inferred based on binomial distribution for each endpoint and 2-sided 95% simultaneous CIs inferred using the Goodman method (Goodman 1965). The Goodman method is used for obtaining simultaneous CIs (better than single binomial CIs) for the parameters of a multinominal distribution, for example for a multinomial endpoint (4-week interval, 8-week interval, 12-week interval, 16-week interval, and 20-week interval). These analyses will be performed for all participants and within the two regimens.

For the analyses of functional and anatomical outcome (i.e., change in CSFT) the 95% CI will be inferred based on ANOVA analyses. The same analysis model as used for change from

baseline in BCVA will be used with the baseline BCVA categories replaced by baseline CSFT categories.

2.6.3 Handling of missing values/censoring/discontinuations

In case of treatment interruption, if the duration of the last interval falls within the following ranges of [q4w, q8w) or [q8w, q12w), [q12w, q16w), [q16w, q20w) or ≥ q20w then the floor value of these ranges i.e., q4w, q8w, q12w, q16w, q20w, respectively, will be used for imputation.

The last potential study treatment may be administered at the Week 52 visit (or at the Week 54 visit for the participants who will have received study treatment at an odd number of inspection visits). Hence throughout this document, analyses based on Week 52 BCVA and other efficacy data are performed if Week 52 data are available. If Week 52 BCVA and other efficacy data are not available, Week 54 BCVA and other efficacy data will be used instead of Week 52. Otherwise, LOCF will be used to impute missing BCVA as per the estimand framework.

For participants who discontinue study treatment but continue in the study, data collected after the switch to alternative treatment in the study eye will be censored for the primary analysis. Censored data will be replaced using LOCF with the last observation collected prior to/on the start of an alternative treatment in the study eye.

2.7 Safety analyses

The following endpoint will be used to assess the safety and tolerability of brolucizumab

- Occurrence of Ocular and Non-ocular AEs up to Week 56.

The primary population for safety analyses is the FAS. Additionally, the Enrollment Set will be used to summarize pre-treatment AEs and all AEs that occur during the extension study. All listings and tables will be presented for all participants.

Safety summaries (tables, figures) will include only data from the baseline of the extension study, which is also EOS/Week 64 of the core study.

2.7.1 Adverse events (AEs)

Note that AEs which start during the core study and end prior to the core EOS are not recorded on the Medical History eCRF, nor the Adverse Event eCRF. These AEs are considered as the Medical History in the extension study, hence the data from the core AE will be programmatically merged with the Medical History eCRF. Therefore, these events are not included in any AE summaries or listings but will be included in Medical History listings.

Treatment-emergent Adverse Events: The primary summaries of AEs will be based on treatment-emergent adverse events (TEAE). A TEAE is defined as any AE that develops on/after the first injection of study treatment or any event already present that worsens following the first injection of study treatment.

The number (and percentage) of participants with TEAEs will be summarized separately for ocular (study eye and fellow eye) and non-ocular in the following ways:

- Overall summary of subjects with death, any TEAE, any severe TEAE, any study treatment related TEAE, any TEAE leading to study treatment discontinuation, any treatment-emergent serious AE (TESAE), any study treatment related TESAE;
- TEAE, TESAE by primary SOC and PT;
- TEAE by primary SOC, PT, and maximum severity
- TEAE by Standardized MedDRA Query (SMQ) and PT;
- TEAEs related to study treatment by primary SOC and PT;
- TEAEs leading to study treatment discontinuation by primary SOC.

A subject with multiple AEs within a primary SOC is only counted once towards the total of the SOC.

Ocular TEAE in the study eye with occurrence greater than or equal to 1% and non-ocular TEAE with occurrence greater than or equal to 2% will be summarized by PT.

Pre-treatment Adverse Events: In addition to TEAEs, AEs which start on/after day 1 of the extension study and prior to the date/time of the first injection of the study treatment in the extension study will be summarized using number and percentage of patients by ocular (study eye and fellow eye)/non-ocular, primary SOC and PT using the Enrollment Set.

Study-emergent Adverse Events: All AEs that occur during the on-treatment period (defined in Section 2.1.1) will be summarized separately for ocular (study eye and fellow eye) and non-ocular events using the Enrollment Set in the following ways:

- AEs by primary SOC and PT;
- SAEs by primary SOC and PT;
- SAEs by primary SOC and PT, and maximum severity;
- Study treatment related SAEs, by primary SOC and PT

All deaths, SAEs or AEs leading to permanent study treatment discontinuation during the study will be summarized.

Adverse events are coded using MedDRA terminology.

For the legal requirements of ClinicalTrials.gov and EudraCT, two tables are mandatory:

- <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than X%. Detailed threshold (X%) will be determined by safety disclosure
- <on-treatment/treatment emergent> serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, 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 / SAE suspected to be related to study treatment / non-SAE has to be checked in a block e.g., among AE's 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.

2.7.1.1 Adverse events of special interest / grouping of AEs.

The number (%) of subjects with treatment-emergent AESIs will be summarized by category and PT.

A Case Retrieval Sheet (CRS) with the exact composition of the AE groupings is to be used to map reported AEs to the AESI groupings. This file may be updated (i.e., it is a living document) based on review of accumulating trial data, and therefore the groupings are also subject to potential change. The most up-to-date version of the CRS will be used at the time of the analysis.

AESIs related to the study treatment and/or study treatment procedure will be summarized by category and PT term.

2.7.2 Deaths

On-treatment deaths and all deaths including those that occurred outside the on-treatment period will be summarized by primary SOC and PT. A listing will also be provided.

2.7.3 Loss in best corrected visual acuity

Number and % of subjects who lost ≥ 15/ ≥ 30 letters in BCVA from baseline up to Week 56 will be presented for the study eye. Missing data will not be imputed. Number of subjects with ≥ 15/ ≥30 letter loss at the last visit will also be summarized. In addition, a listing for subjects who lost ≥ 15/ ≥ 30 letters in the study eye from the baseline at Week 56 will be provided.

2.7.4 Laboratory data

Not applicable.

2.7.5 Other safety data

2.7.5.1 Vital signs

Summary statistics of vital signs will be provided based on data from the on-treatment period excpet for baseline data which will be summarized where appropriate.

Clinically relevant abnormalities in vital signs data i.e., sitting blood pressure (systolic and diastolic pressure in mmHg) and pulse rate (beats per minute) will be listed by subject, and visit/study day and abnormalities as per normal range and critical values as per Table 2-2 will be flagged.

Number (%) of participants with critical abnormalities will also be provided.

Table 2-2 Critical changes in vital signs

Variable	Category	Critical Values

Systolic blood pressure (mmHg)	High	Either > 180 with an increase from baseline of the extension study > 30 or > 200 absolute
	Low	Either < 90 with a decrease from baseline of the extension study > 30 or < 75 absolute
Diastolic blood pressure (mmHg)	High	Either > 105 with an increase from baseline of the extension study > 20 or > 115 absolute
	Low	Either < 50 with a decrease from baseline of the extension study > 20 or < 40 absolute
Pulse rate (bpm)	High	Either > 120 with an increase from baseline of the extension study > 25 or > 130 absolute
	Low	Either < 50 with a decrease from baseline of the extension study > 30 or <40 absolute

Summary statistics will also be provided by visits.

Intraocular pressure (IOP) measurements will be recorded in mmHg.

Summary statistics of pre-dose observed IOP values and change from baseline of the extension study for both study and fellow eyes will be presented by visit.

Furthermore, summary statistics of pre-dose and post-dose observed IOP values and respective change from pre-dose for the study eye will be presented by visit.

Listing of clinically significant elevations in pre- and post-dose IOP measurements for both study and fellow eyes will be provided by visit/study day and elevated IOPs (≥ 25 mmHg) will be flagged.

2.8 Pharmacokinetic endpoints

Not applicable.

2.9 PD and PK/PD analyses

Not applicable.

2.10 Patient-reported outcomes

Not applicable.

2.11 Biomarkers

Not applicable.

[redacted]

[redacted]

2.13 Interim analysis

Not applicable.

3 Sample size calculation

All participants who completed Week 64/EOS in the core study and meet all inclusion and exclusion criteria will be eligible for enrollment into the extension study. The initial sample size analyses assumed that all participants completing the core study and eligible for enrollment in the extension study will be enrolled in the extension study. After the protocol amendment, it is planned that approximately 250 participants will be enrolled the extension study. Simulation studies conducted before the urgent safety measures were introduced are described below.

Table 3-1 shows the distribution of duration as estimated based on simulation studies along with precision as estimated based on the simulations. Table 3-2 shows width of 95% CI as estimated based on a sample of size (number of participants completing the extension study) varying from 503 to 100. The numbers are chosen based on assuming that 90%/80%/70%/etc of participants from the core study enter the extension and also assuming that 10%/20%/30%/etc of participants drop out reaching EOS of the extension. Similarly, Table 3-3 shows 95% CI for the estimate in the change of BCVA, assuming that the observed change is -1 and the standard deviation of the change is 13.

For example, when the number of participants completing the extension study decreases from 503 to 212, width of the 95% CI increases from 5.8% to 9% for the estimated proportion of 12.7% participants being on the 16-weeks interval; and from 6.9% to 9.8% for the estimated proportion of 19.4% of participants being on 20-weeks interval. With the same reduction in the sample size, the 95% CI for the estimated change in BCVA goes from (-2.1, 0.14) to (-2.8, 0.8).

The 95% CI are obtained using PASS 11.

Table 3-1 Duration of intervals as estimated based on simulation studies

Interval duration	4-weeks	8-weeks	12-weeks	16-weeks	20-weeks
Frequency (SD as assesed by simulations)	8.6% (1.7%)	30.2% (1.9%)	29.2% (2.3%)	12.7% (1.7%)	19.4% (2.4%)

Table 3-2 Duration of intervals as estimated based on simulation studies and width of 95% confidence Interval

Duration of the treatment interval	**4-weeks**	**8-weeks**	**12-weeks**	**16-weeks**	**20-weeks**
Frequency (SD from simulations)	8.6% (1.7%)	30.2% (1.9%)	29.2% (2.3%)	12.7% (1.7%)	19.4% (2.4%)
N of participants completing the extension study	**Width of 95% Confidence Interval**				
503	4.9%	8.0%	7.9%	5.8%	6.9%
447	5.2%	8.5%	8.4%	6.2%	7.3%
391	5.6%	9.1%	9.0%	6.6%	7.8%
348	5.9%	9.6%	9.6%	7.0%	8.3%
304	6.3%	10.3%	10.2%	7.5%	8.9%
250	7%	11.4%	11.3%	8.3%	9.8%
212	7.5%	12.4%	12.2%	9%	10.6%
200	8.3%	13.1%	13.0%	9.7%	11.4%
170	9.0%	14.3%	14.2%	10.6%	12.4%
150	9.6%	15.2%	15.1%	11.3%	13.2%
120	10.9%	17.1%	16.9%	12.7%	14.9%
100	12.0%	18.8%	18.6%	14.0%	16.3%

Table 3-3 95% Confidence interval for BCVA change assuming SD of the change is 13

N of participants completing the extension study	95% Confidence Interval of BCVA change assuming the observed change is -1.
503	(-2.1, 0.14)
447	(-2.2, 0.21)
391	(-2.3, 0.29)
348	(-2.4, 0.37)
304	(-2.5, 0.47)
250	(-2.6, 0.62)
212	(-2.8, 0.76)
200	(-2.8, 0.81)
170	(-3.0, 0.97)
150	(-3.1, 1.1)
120	(-3.4, 1.4)
100	(-3.6, 1.6)

4 Change to protocol specified analyses

Added in the SAP is the secondary endpoint characterizing the change from the baseline of the core study for all participants and per randomized arm in the core study. Specifically,

- Change in CSFT from the baseline of the core study by visit.
- Average change in CSFT from the baseline of the core study at Week 52 and Week 56.
- Change in BCVA from the baseline of the core study by visit.
- Average change in BCVA from the baseline of the core study at Week 52 and Week 56.

Statistical analyses are described in Section 2.6.1.

BCVA categories are the same as in the SAP for the core study.

5 Appendix

5.1 Imputation rules

Not applicable.

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

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.

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.

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

	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 -

1. 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.
2. 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).
3. 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).
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.

5.1.3 Concomitant medication 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 follow up period date, 31DECYYYY, and 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 follow up period 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.

Concomitant medication start date imputation

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)** Uncertain	**(1)** Uncertain	**(1)** Uncertain	**(1)** Uncertain
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.a)** 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.

5.1.3.1 Prior therapies date imputation

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Other imputations

Not applicable.

5.2 AEs coding/grading

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

The below severity grade will be used in this study:

- Mild: usually transient in nature and generally not interfering with normal activities
- Moderate: sufficiently discomforting to interfere with normal activities
- Severe: prevents normal activities

5.3 Laboratory parameters derivations

Not applicable.

5.4 Statistical models

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

The classification in Table 5-1 will be used for the analysis sets. Participants with PDs as per the PD specification document will be excluded from the PPS.

Table 5-1 Patient classification

Analysis Set	PD ID that cause participants to be excluded	Non-PD criteria that cause participants to be excluded
FAS	P_INCL01_ICF not obtained before start	Not in Randomized Analysis Set;
PPS	P_INCL01_ICF not obtained before start M_INCL03_No Active CNV secondary to AMD M_INCL04_Absence of IRF/SRF study eye M_EXCL01_Confounding condition study eye M_EXCL03_Confound med/procedure study eye M_EXCL04_Confound syst condition or Trt M_EXCL07_Systemic investigational drugs M_OTH02_Trt interval wrongly adjusted M_COMD01_Prohibited meds or procedure M_TRT04_Under Treatment M_TRT05_Over Treatment	Not in FAS AR_EST_01 AR_ETD_01 AR_MD_01

Analysis Set	PD ID that cause participants to be excluded	Non-PD criteria that cause participants to be excluded
	M_OTH08_Any other PD with impact	

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

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

Table 5-1 Non-protocol deviations (analysis restrictions)

AR ID	Description of AR	Inclusion/Exclusion in Analysis
AR_EST_01	Early study termination due to reasons other than lack of efficacy/safety	Exclude from PPS
AR_ETD_01	Early study treatment termination due to reasons other than lack of efficacy/safety	Exclude from PPS analyses
AR_MD_01	No valid BCVA assessment between Week 52 and Week 56	Exclude from PPS analysis

6 Reference

Goodman, LA (1964) Simultaneous Confidence Intervals for Contrasts Among Multinomial Populations. Ann. Math. Statist; 35 (2):716--725. doi:10.1214/aoms/1177703569.