Official Title: A Real-world, Prospective, Multi-center, Open-label, Phase IV Clinical Study to Evaluate Evaluate the Safety and Effectiveness of Intravitreal Injections (IVI) of Brolucizumab in Patients With Neovascular Age-related Macular Degeneration (nAMD)

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STATISTICAL ANALYSIS PLAN

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Glossary of abbreviations

ABBREVIATION	DESCRIPTION
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
CI	Confidence interval
CV	Coefficient of variation
CRF	Case Report/Record Form
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database lock
eCRF	Electronic case report form
FAS	Full Analysis Set
ICH	International Conference on Harmonisation
IRF	Intra-retinal fluid
IVI	Intravitreal Injections
LOCF	Last Observation Carried Forward
MedDRA	Medical dictionary for regulatory activities
N	Sample size
nAMD	Neovascular Age-related Macular Degeneration
OCT	Optical Coherence Tomography
ODS	Output delivery system
PT	Preferred term
q8w	8-week injection interval
q12w	12-week injection interval
RTF	Rich text format
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCR	Screening Analysis Set
SD	Standard deviation
SOC	System organ class
SRF	Sub-retinal fluid
TEAEs	Treatment-emergent adverse events
TLFs	Tables, data listings and figures
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

1. Overview

1.1 Introduction

This document describes the rules and conventions to be used in the presentation and analysis of intravitreal injections (IVI) of brolucizumab in patients with neovascular age-related macular degeneration (nAMD).

This statistical analysis plan (SAP) is based on protocol CRTH258AIN01, 0.2, dated 06-May-21.

2. Trial objectives

The purpose of this study is to generate additional safety and effectiveness data in Indian nAMD patients that more closely resemble the real-world population intended to be treated with brolucizumab.

This study is being conducted as part of the post-marketing regulatory commitment to the Indian Health authority.

The following objectives are those stated in the protocol.

2.1 Primary objective

1 To evaluate ocular & non-ocular safety of intravitreal brolucizumab in real-world patients with nAMD

2.2 Secondary objectives

1 To evaluate the effectiveness of brolucizumab in the management of nAMD in terms of change in best-corrected visual acuity (BCVA) from baseline to Week 56
2 Characterize the number of anti-VEGF injections, number of non-injection visits, and total number of visits during the 56 weeks of treatment with brolucizumab.
3 Estimate the percentage (%) of patient eyes with anti-VEGF injection intervals q8w and q12w during the 56 weeks of treatment with brolucizumab.
4 Estimate effect of brolucizumab on fluid from baseline to week 16 and week 56.
5 Estimate effect of brolucizumab on central subfield thickness (CST) from baseline to week 16 and week 56.

3. Endpoints

3.1 Primary endpoint

1 Incidence and characteristics of treatment-emergent adverse events during the 56 weeks of treatment with brolucizumab.

3.2 Secondary endpoints

1a. Mean change in BCVA from baseline to week 16 and week 56 as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters.

1b. Percentage (%) of patient eyes with gain in BCVA of 15/10/5 ETDRS letters or more from baseline to week 16 and week 56.

1c. Percentage (%) of patient eyes with loss in BCVA of 15/10/5 ETDRS letters or more from baseline to week 16 and week 56.

2. Number of anti-VEGF injections, non-injection visits and total number of visits during the 56 weeks of treatment with brolucizumab.

3a. Percentage (%) of patient eyes with at least one duration of interval between injections ≥ 8 weeks but <12 weeks.

3b. Percentage (%) of patient eyes with at least one duration of interval between injections ≥ 12 weeks.

4a. Absence of intra-retinal fluid from baseline to week 16 and week 56.

4b. Absence of sub-retinal fluid from baseline to week 16 and week 56.

5. Estimate CST change from baseline (in µm) to week 16 and at week 56.

4. Trial design

4.1 Design overview

This is a prospective, multi-center, open-label, interventional phase IV clinical study. All patients with nAMD who are planned to be treated with brolucizumab and have provided informed consent may be enrolled in this study. The treatment period for each patient will be 56 weeks after the start of brolucizumab treatment. Study visits will be scheduled at week 4, week 8, week 16, and thereafter at intervals of 8 weeks or 12 weeks after disease activity assessment at week 16.

Brolucizumab 6 mg will be administered by IVI injection as per the Prescribing information (PI) and in line with the treating physician's clinical judgement. Patients will receive loading doses of brolucizumab at Day 0/Visit 1, Week 4/Visit 2 and Week 8/Visit 3. After the loading doses, at Week 16, disease activity assessment (DAA) will be performed based on BCVA and OCT to assess whether the patient will require q8w or q12w dosing.

Patients who are scheduled for q8w dosing with brolucizumab will receive injections at weeks 16, 24, 32, 40, 48. Patients who are scheduled for q12w dosing of brolucizumab will receive injections at weeks 20, 32, and 44. Data will be conducted as per the q8w and q12w dosing administration. Allocation and re-allocation to q8w/q12w dosing regimen will be as per Investigator's discretion.

4.2 Schedule of events

Refer to section 7.3.7 "Table 7-1 Data Collection" of study protocol.

5. Changes/deviations from the planned analysis

Analysis will be performed as per planned protocol however, if any deviation in implementing original statistical plan will be described and justified in the clinical study report.

6. Analysis population

Agreement and authorization of patients included/excluded from each analysis population will be reached prior to final database hard lock. Sponsor will review and confirm a list of all patients to be excluded from the relevant analysis populations, including the reason(s) for exclusion from the analysis populations. All safety and effectiveness analyses will use the Full Analysis Set (FAS).

6.1 Screening Analysis Set (SCR)

All patients who signed the informed consent form.

6.2 Full Analysis Set (FAS)

The Full Analysis Set (FAS) will consist of all patients who provided informed consent and are treated with at least one dose of brolucizumab in this interventional study.

7. General considerations

7.1 Visit and date conventions

The assigned nominal visit will be used for by-visit summaries. Unscheduled measurements will not be included in by-visit summaries. Data listings will include scheduled, unscheduled, and early discontinuation data. Trial visit will be assigned as delineated in Table 7-1 from protocol.

7.2 Baseline

Baseline is defined as the last non-missing observation made prior to the first administration of Brolucizumab.

7.3 Stratifications

For analysis purposes, trial patients may be sub-classified into the following stratification levels, where applicable:

- Dosing interval post loading dose
  - q8w dosing
  - q12w dosing

7.4 Statistical tests

The default significance level for this trial is set at 5%. All 95% confidence intervals (CIs) and statistical tests will be two-sided, unless otherwise specified. The statistical test like Clopper Pearson test and Paired t-test will be performed.

7.5 Common calculations

Summary statistics for continuous variables will include the number of observations (n), arithmetic mean, standard deviation (SD), minimum, lower quartile, median, upper quartile and maximum. Categorical variables will be presented with absolute and relative frequencies. In addition, key results will be presented with two-sided 95% confidence intervals and p-values for within-patient changes across time.

7.6 Interim Analysis

An interim safety analysis will be performed for the first 50 patients and a quarterly interim safety report will be submitted to the Indian Regulatory Authority, as per their requirements. A complete analysis will be done after all enrolled patients complete the 56 weeks study period or discontinue the study prior to week 56.

Manual Report will be submitted based on eDC data includes site status, enrolment status and AE list.

7.7 Software

All analyses will be conducted using SAS® Version 9.4 or later.

8. Statistical considerations

8.1 Multicentre studies

The study plans to enrol a total of 105 patients in 11 centres. 105 patients have been enrolled from 10 initiated sites.

8.2 Missing data

If no post-baseline value is available for a parameter, then the patient will be removed from the analysis of respective parameter. Otherwise, if at least one post-baseline value is available, missing values will be imputed by the last observation carried forward (LOCF) principle regardless of the reason for missing data. Partial date imputation will be performed for the concomitant medication data.

9. Protocol deviations

9.1 Variables and derivations

Protocol deviation related data will be captured by clinical team in the external log and this external log will be used for analysis.

9.2 Analysis

Population:	FAS
Stratification:	Table: NA Listing: By patient no. and start date
Statistics:	The protocol deviations (patient wise PD list) will be summarized (frequency and percentage). The patient wise PD listings will be presented along with site wise PDs list (if applicable).

10. Participant disposition and withdrawal

10.1 Variables and derivations

End of trial classifications are defined as follows:

- Screening failure: Patient signed an informed consent form but has not satisfied inclusion and exclusion criteria.
- Enrolled Patients: Patient signed an informed consent form and has satisfied inclusion and exclusion criteria.
- Discontinued patients: patients who discontinued the trial, as indicated in the "Study Completion" eCRF form, will be assumed to be discontinued patients
- Completed trial: Patients who completed the trial, as indicated in the "Study Completion" eCRF form, will be assumed to have completed the trial.

The following parameters will be summarised for the patient's disposition table as per eCRF

- Number of screened patients
- Number of screening failure patients
- Number of enrolled patients
- Number of patients enrolled but not received the first dose of Brolucizumab
- Number of patients received all dose of Brolucizumab
- Full analysis Set (FAS)
- Number of completed patients
- Number of discontinued patients

  Patient's primary reason for discontinuation (reasons mentioned in eCRF study completion form) which is as follows:

  - Adverse event
  - Unsatisfactory therapeutic effect
  - Subject's condition no longer requires study treatment
  - Subject withdrew consent
  - Lost to follow-up
  - Administrative Problems
  - Switch Agent
  - Death
  - Other

Derivation:

- If patient status is indicated as “screen failure” in the eCRF screen failure form, then respective patients will be counted as screen failure.
- If the question “Was written informed consent obtained” = “Yes” from the informed consent eCRF form and the question “Did the subject meet all eligibility criteria” = “Yes” then respective patients will be counted as enrolled patients.
- If the question “Did the patient complete the study” = “No” from the Study Completion eCRF form, then respective patients will be counted as discontinued patients.
- If the question “Did the patient complete the study” = “Yes” from the Study Completion eCRF form, then respective patients will be counted as completed patients.

10.2 Analysis

Population:	SCR
Stratification:	Table: NA Listing: By patient no.
Statistics:	Patient’s disposition and early withdrawal will be summarised (frequency and percentages based on patients received the first dose of Brolucizumab) for all categories except the screened, screen failure, enrolled, patients enrolled but not received the first dose of Brolucizumab will be summarised (frequency) by total for table. The listing will be provided for the patient’s disposition status and early withdrawal patients separately.

11. Participant demographics and other baseline characteristics

11.1 Variables and derivations

The following demographic and other baseline characteristics will be summarized by treatment group:

- Age (Years)
- Gender (Male and Female)
- Nationality
- Race
- Ethnicity
- Height (cms) at Screening
- Weight (kgs) at Screening
- Smoking history (Current Smoker, Past Smoker and Never Smoker)
- Baseline value of BCVA
- Risk factors and ocular disease related history
- Patients with treatment for nAMD received in the 12 months prior to study entry

11.2 Analysis

Population:	For Table: FAS For Listing: SCR
Stratification:	Table: NA Listing: By patient no.
Statistics:	Demographic and other baseline characteristics will be summarized for table and presented in data listings.

12. Exposure and Compliance to the study treatment

12.1 Variables and derivations

In “Brolucizumab dosing” eCRF form treatment dosing related data will be captured. The following parameters will be summarised for treatment exposure:

- Number of patients received Brolucizumab dose by visit
- Number of patients received the doses under q8w dosing interval
- Number of patients received the doses under q12w dosing interval
- Number of patients received all planned doses.
- Duration of exposure between first and last doses (Days)

The parameter “Compliance with overall treatment” will be summarised for treatment compliance.

Patient will be considered compliant with overall treatment Brolucizumab if they received the scheduled administration of all doses within the schedule visits and time window.

12.2 Analysis

Population:	For Table: FAS For Listing: SCR
Stratification:	Table: NA Listing: By patient no.
Statistics:	Treatment exposure and compliance will be summarised (frequency and percentages) for table and the listing will be presented.

13. Medical and treatment history

13.1 Variables and derivations

Medical history data will be coded using the MedDRA central coding dictionary, Version 24.1 or later.

The following parameters will be summarised for the subject's medical history as mentioned in eCRF.

- Number of patients with at least one medical history
- Number of patients for each medical history by SOC and PT

13.2 Analysis

Population:	For Table: FAS For Listing: SCR
Stratification:	Table: NA Listing: By patient no. and alphabetically for SOC and PT within each SOC
Statistics:	Medical history will be summarised (frequency and percentages) for table. Medication History for nAMD will also be presented in the table separately. Listing will be provided.

14. Prior and Concomitant medications

14.1 Variables and derivations

In eCRF “Prior and Concomitant Medications” form concomitant medication related data will be captured.

All prior and concomitant medications entered into the database will be coded using the WHODD B3, dated September 1, 2021 or later. Preferred ATC coding will be applied to medications.

‘Prior medications’ are defined as any medication started and ended prior to first administration of the Brolucizumab dose.

Concomitant medications are defined as any medication taken after or on the first administration of the Brolucizumab dose till the end of the trial or any medication taken prior to the first Brolucizumab dose administration and having “ONGOING” status at the first administration of the Brolucizumab dose.

In section 24 Appendix 2 the algorithm is given for calculation of partial date imputation for Concomitant Medication, and it will be used for partially missing Concomitant Medication start and end date imputation.

The following parameters will be summarised for the patient’s prior and concomitant medication:

- Number of patients with at least one prior and concomitant medication
- Number of patients for each prior and concomitant medication by ATC-2 and PT.

Derivations:

All medications captured on the “Prior and Concomitant Medications” form of the eCRF will be categorised (prior and concomitant medication) as follows:

- If the medication end date is less than the first Brolucizumab dose administration date, then respective medication will be considered as “Prior Medication”.
- If the medication start date or end date is greater than or equal to the first Brolucizumab dose administration date or if the medication start date is less than the first Brolucizumab dose administration date and medication is marked

as “ONGOING” then respective medication will be considered as “Concomitant Medication”.

14.2 Analysis

Population:	For Table: FAS For Listing: SCR
Stratification:	Table: by descending frequency of ATC-2 level and PT within each ATC-2 level Listing: By patient no. and start date
Statistics:	Prior and concomitant medication will be summarized as (frequency and percentages) for table and listing will be provided. In addition, the number and percentage of patients receiving rescue medications and significant non-drug therapy will be summarized by preferred term (coded by WHO ATC classification) and the same will be listed.

15. Adverse events

15.1 Variables and derivations

Adverse Events (AEs) will be coded using medical dictionary for regulatory activities (MedDRA) terminology, Version 24.1 or later.

An AE is any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the event is not considered to be treatment related.

The following parameters will be summarised for the overview of patient's adverse events:

- Incidence of AEs
- AEs related to Brolucizumab
- Ongoing AEs (if applicable)
- CTCAE grade of AEs
  - Mild
  - Moderate
  - Severe
  - Life Threatening
  - Death Related to AE
- Serious adverse event
- Serious AEs related to Brolucizumab
- AEs Action Taken
  - No action taken
  - Investigational treatment permanently discontinued due to this adverse event
  - Concomitant medication given
  - Non-drug therapy given
  - Patient hospitalized/ patient hospitalization prolonged
- Outcome of AEs
  - Not Recovered or Not Resolved
  - Recovered or Resolved
  - Recovering or Resolving
  - Recovered Or Resolved with Sequelae
  - Fatal
  - Unknown

- AEs leading to Discontinuation from the study
- AEs leading to Death
- Related AEs leading to Death

The overview of serious adverse events will also be summarised using the above-mentioned parameters with one additional “seriousness criteria” category which includes (death, life threatening, Involved or prolonged inpatient hospitalization, Results in persistent or significant disability / incapacity, Congenital anomaly/birth defect, medically significant event) will be provided in the table.

Derivations:

- The question “Relationship to study drug” is answered as “Yes” then respective AEs will be considered as Related AE.
- The question “Was the adverse event serious” is answered as “YES” then respective AE will be considered as serious AEs.
- Subject’s primary reason for discontinuation is “Adverse Event” then we will consider it as AEs leading to Discontinuation from the study.
- Subject’s primary reason for discontinuation is “Death” or AE Outcome is “FATAL” then we will consider it as AEs leading to death.
- Subject’s primary reason for discontinuation is “Death” or AE Outcome is “FATAL” and “Relationship to study drug” is answered as “Yes” then we will consider it as Related AEs leading to death.

15.2 Analysis

Uncoded adverse events category will be added in the AEs by SOC/PT summary tables if applicable.

The analysis of incidences of TEAEs, Ocular and systemic AEs, Suspected AEs related to the study medication, Serious AEs, AEs leading to death, AEs leading to discontinuation from the study by primary system organ class and preferred term is covered in the primary endpoint section 19.

15.2.1 Overview summary for AEs and SAEs

Population:	For Table: FAS For Listing: SCR
Stratification:	Table: NA. Listing: By patient no.
Statistics:	An overview summary will be presented as (n=number of patients, m=number of events and %=percentage of patients) for table. The listings will be presented

15.2.2 Incidence of serious adverse event, AEs suspected to be related to the study drug, AEs leading to discontinuation from the study, TEAEs leading to death by severity

Population:	For Table: FAS For Listing: SCR
Stratification:	Table: by descending frequency of SOC and descending frequency of PT within each SOC and severity.
Statistics:	All AEs categories mentioned above will be summarized for table.

16. Safety laboratory tests

The Safety laboratory data will not be applicable for this study.

17. Vital signs

17.1 Variables and derivations

In “vital signs” eCRF form vital signs at baseline related data will be captured.

The following vital signs will be reported for this study:

- Heart rate (bpm)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

The qualitative measurements of vital signs will be categorised as (Normal, Abnormal Clinically Significant and Abnormal Not Clinically Significant)

17.2 Analysis

Population:	For Table: FAS For Listing: SCR
Stratification:	Table: NA Listing: By patient no. and visit
Statistics:	The quantitative and qualitative data will be summarized in table. listing will be presented.

18. Physical examination

18.1 Variables and derivations

In “Physical examination” eCRF form physical examination at baseline related data will be captured.

The physical examination including the following body systems will be examined:

- Ears, Eyes, Nose, Throat and Neck
- Lymph nodes
- Lungs
- Heart
- Abdomen
- Skin
- Extremities
- Neurological System
- Musculoskeletal Systems
- Other

These measurements will be categorised as (Normal, Abnormal Clinically Significant, Abnormal Not Clinically Significant and Not Done)

18.2 Analysis

Population:	For Table: FAS For Listing: SCR
Stratification:	Table: NA Listing: By patient no. and visit
Statistics:	Physical examination data will be summarized (frequency and percent) and listed.

19. Primary endpoint assessments

The primary endpoint will evaluate the safety of intravitreal brolucizumab in real-world patients with nAMD.

19.1 Incidence and characteristics of treatment-emergent adverse events during the 56 weeks of treatment with brolucizumab

19.1.1 Variables and derivations

Variables:

The following incidences of TEAEs during the 56 weeks of treatment and its characteristics will be reported:

- Incidences of TEAEs
- Ocular and systemic AEs
- Suspected AEs related to the study medication
- Serious AEs
- AEs leading to death
- AEs leading to discontinuation from the study

Derivation:

- Timeframe: The first brolucizumab administration date to Visit 11 (week 56)
- If the question from eCRF, “Treatment Emergent AE” = “Yes”, then corresponding events will be considered as TEAEs.
- Ocular and systemic AEs.
- If the question from eCRF, “Relationship with study drug” = “Yes”, then corresponding events will be considered as suspected AEs related to the study medication.
- If the question from eCRF, “Was the adverse event serious” = “Yes”, then corresponding events will be considered as serious AEs.
- If the question from eCRF, “What is the outcome of this adverse event” = “Fatal”, then corresponding events will be considered as AEs leading to death.
- If the question, “Primary Reasons for Discontinuation” = “Adverse event”, then corresponding events will be considered as AEs leading to discontinuation from the study.

19.1.2 Primary analysis

Population: FAS

Stratification: Table: Descending frequency of SOC and descending frequency of PT within each SOC.

Statistics: The incidence of TEAEs and its characteristics (i.e., Ocular and systemic AEs, Suspected treatment emergent AEs related to the study medication, Serious treatment emergent AEs, TEAEs leading to Death, TEAEs leading to discontinuation of study,) will be summarised for table as number of patients (n), percentages (%) and number of events (m). TEAEs will also be summarized by primary system organ class, preferred term and severity.

20. Secondary endpoint assessments

The secondary endpoints will evaluate the effectiveness of brolucizumab.

20.1 Mean change in BCVA from baseline to week 16 and week 56 as measured by Early Treatment Diabetic Retinopathy Study (ETDRS) letters

20.1.1 Variables and derivations

Variables:

- Total Visual Acuity Score (ETDRS letters)

Derivations:

- Time Frame: Baseline to week 16 and Baseline to week 56.
- If the question “select the Assessment” is answered as “Total Visual Acuity Score (ETDRS letters)” from BCVA form of eCRF then corresponding results will be used from total Visual Acuity Score (ETDRS letters) for study eye.

20.1.2 Analysis

Population:	For Table: FAS For Listing: SCR
Stratification:	Table: NA Listings: By patient no. and date of test
Statistics:	The summary statistics for absolute and absolute change from baselines will be presented in the table as number of observations (n), arithmetic mean, standard deviation (SD), lower quartile, median, upper quartile, minimum and maximum. Point estimate, Two-sided 95% confidence intervals and p-values for within-patient changes across time will be presented using paired t-test. The listing will be presented.

20.2 Percentage (%) of patient eyes with gain in BCVA of 15/10/5 ETDRS letters or more at week 16 and week 56

20.2.1 Variables and derivations

Variables:

- Total Visual Acuity Score (ETDRS letters)

Derivations:

- If the question “select the Assessment” is answered as “Total Visual Acuity Score (ETDRS letters)” from BCVA form of eCRF then corresponding results will be used from total Visual Acuity Score (ETDRS letters) for study eye as appropriate.
- Below mentioned categories will be derived as follows:
    - Gain in BCVA of 15 ETDRS letters: If the Total Visual Acuity Score (ETDRS letters) >= 15 ETDRS letters then corresponding patients will be considered as “Gain”
    - Gain in BCVA of 10 ETDRS letters: If the Total Visual Acuity Score (ETDRS letters) >= 10 ETDRS letters then corresponding patients will be considered as “Gain”
    - Gain in BCVA of 5 ETDRS letters: If the Total Visual Acuity Score (ETDRS letters) >= 5 ETDRS letters then corresponding patients will be considered as “Gain”

20.2.2 Analysis

Population:	FAS
Stratification:	Table: NA
Statistics:	Number of patient (n) and percentage (%) will be presented for patient eyes with gain in BCVA of 15, 10 and 5 ETDRS letters categories or more at week 16 and week 56 in table. 95% Confidence interval will be calculated and presented using Clopper Pearson test.

20.3 Percentage (%) of patient eyes with loss in BCVA of 15/10/5 ETDRS letters or more at week 16 and week 56

20.3.1 Variables and derivations

Variables:

- Total Visual Acuity Score (ETDRS letters)

Derivations:

- If the question “select the Assessment” is answered as “Total Visual Acuity Score (ETDRS letters)” from BCVA form of eCRF then corresponding results will be used from total Visual Acuity Score (ETDRS letters) for study eye.
- Below mentioned categories will be derived as follows:
    - Loss in BCVA of 15 ETDRS letters: If the Total Visual Acuity Score (ETDRS letters) < 15 ETDRS letters then corresponding patients will be considered as “Loss”
    - Loss in BCVA of 10 ETDRS letters: If the Total Visual Acuity Score (ETDRS letters) < 10 ETDRS letters then corresponding patients will be considered as “Loss”
    - Loss in BCVA of 5 ETDRS letters: If the Total Visual Acuity Score (ETDRS letters) < 5 ETDRS letters then corresponding patients will be considered as “Loss”.

20.3.2 Analysis

Population:	FAS
Stratification:	Table: NA
Statistics:	Number of patient (n) and percentage (%) will be presented for patient eyes with loss in BCVA of 15, 10 and 5 ETDRS letters categories or more at week 16 and week 56 in table. 95% Confidence interval will be calculated and presented using Clopper Pearson test.

20.4 Number of anti-VEGF injections, non-injection visits, and total number of visits during the 56 weeks of treatment with brolucizumab.

20.4.1 Variables and derivations

Variables:

- Date of Brolucizumab Administration
- Date of Visit

Derivations:

- The total number of Brolucizumab anti-VEGF injections and non-injection visits will be calculated using Brolucizumab dosing form of eCRF if the date of Brolucizumab Administration is not missing on the respective treatment visit then count of injection =1, it will be calculated for all treatment visits and then sum will be calculated to get the number of anti-VEGF injections for respective patient.

20.4.2 Analysis

Population:	For Table: FAS For Listing: SCR
Stratification:	Listing: By patient no. and visit.
Statistics:	Number of anti-VEGF injections, non-injection visits, and total number of visits during the 56 weeks of treatment with brolucizumab will be presented in listing.

20.5 Percentage (%) of patient eyes with at least one duration of interval between injections ≥ 8 weeks but <12 weeks

20.5.1 Variables and derivations

Variables:

- Date of Brolucizumab Administration
- Dosing Schedule (q8w dosing)

Derivations:

If the question from eCRF “Select Dosing Schedule” is answered as “q8w Dosing” and the duration of interval between injections is 8 to 11 weeks.

20.5.2 Analysis

Population:	FAS
Stratification:	Table: NA
Statistics:	Number of patient (n) and percentage (%) will be summarised for the patient eyes with at least one duration of interval between injections ≥ 8 weeks but <12 weeks.

20.6 Percentage (%) of patient eyes with at least one duration of interval between injections ≥ 12 weeks

20.6.1 Variables and derivations

Variables:

- Date of Brolucizumab Administration
- Dosing Schedule (q12w dosing)

Derivations:

If the question from eCRF “Select Dosing Schedule” is answered as “q12w Dosing” and the duration of interval between injections is above or equal to 12 weeks.

20.6.2 Analysis

Population:	FAS
Stratification:	Table: NA
Statistics:	Number of patient (n) and percentage (%) will be summarised for the patient eyes with at least one duration of interval between injections ≥ 12 weeks.

20.7 Percentage of patients with absence of intra-retinal fluid (IRF) from baseline to week 16 and week 56

20.7.1 Variables and Derivations

Variables:

- Intra-retinal fluid results from optical coherence tomography eCRF form

Derivations:

Time Frame: Baseline to week 16 and Baseline to week 56

For baseline visit, if “Intra-retinal fluid Results” is reported as “Absent” then

- At week 16 and week 56, If “Intra-retinal fluid Results (Post Baseline)” is reported as “Same as baseline” then corresponding results will be considered as “Absence” of intra-retinal fluid.
- At week 16 and week 56, If “Intra-retinal fluid Results (Post Baseline)” is reported as (“Increased” or “Present”) then corresponding results will be considered as “Increased” of intra-retinal fluid.

And

For baseline visit, if “Intra-retinal fluid Results” is reported as “Present” then

- At week 16 and week 56, If “Intra-retinal fluid Results (Post Baseline)” is reported as “Completely resolved” then corresponding results will be considered as “Absence” of intra-retinal fluid.
- At week 16 and week 56, If “Intra-retinal fluid Results (Post Baseline)” is reported as “Decreased” then corresponding results will be considered as “Decreased” of intra-retinal fluid.

20.7.2 Analysis

Population:	FAS
Stratification:	Table: NA
Statistics:	Number of patient (n) and percentage (%) will be presented for patients with absence of IRF from baseline to week 16 and week 56.

Additionally, number of patient (n) and percentage (%) for patients with increased and decreased IRF from baseline to week 16 and week 56 will be presented.

20.8 Percentage of patients with absence of sub-retinal fluid (SRF) from baseline to week 16 and week 56

20.8.1 Variables and Derivations

Variables:

- Sub-retinal fluid results from optical coherence tomography eCRF form

Derivations:

Time Frame: Baseline to week 16 and Baseline to week 56

For baseline visit, if “Sub-retinal fluid Results” is reported as “Absent” then

- At week 16 and week 56, If “Sub-retinal fluid Results (Post Baseline)” is reported as “Same as baseline” then corresponding results will be considered as “Absence” of Sub-retinal fluid.
- At week 16 and week 56, If “Sub-retinal fluid Results (Post Baseline)” is reported as (“Increased” or “Present”) then corresponding results will be considered as “Increased” of Sub-retinal fluid.

And

For baseline visit, if “Sub-retinal fluid Results” is reported as “Present” then

- At week 16 and week 56, If “Sub-retinal fluid Results (Post Baseline)” is reported as “Completely resolved” then corresponding results will be considered as “Absence” of Sub-retinal fluid.
- At week 16 and week 56, If “Sub-retinal fluid Results (Post Baseline)” is reported as “Decreased” then corresponding results will be considered as “Decreased” of Sub-retinal fluid.

20.8.2 Analysis

Population:	FAS
Stratification:	Table: NA
Statistics:	Number of patient (n) and percentage (%) will be presented for patients with absence of SRF from baseline to week 16 and week 56. Additionally, number of patient (n) and percentage (%) for patients with increased and decreased SRF from baseline to week 16 and week 56 will be presented.

20.9 Estimated change in CST (in µm) from baseline to week 16 and week 56

20.9.1 Variables and Derivations

Variables:

- Central Subfield Retinal Thickness Results (in µm)

Derivations:

- Time Frame: Baseline to week 16 and Baseline to week 56.

Note: Data of study eye type (i.e., right, or left) will be used in post baselines visit then respective baseline study eye type data will be considered for the analysis.

20.9.2 Analysis

Population:	For Table: FAS For Listing: SCR
Stratification:	Table: NA Listings: By patient and date of test
Statistics:	The summary statistics for absolute and absolute change from baselines will be presented in the table as number of observations (n), arithmetic mean, standard deviation (SD), lower quartile, median, upper quartile, minimum and maximum. Point estimate, Two-sided 95% confidence intervals and p-values for within-patient changes across time will be presented using paired t-test. The listing will be presented.

21. Other assessments

The following assessments will be presented in data listings as per eCRF for the SCR population:

- Fundus Photography
- Fluorescein Angiography

22. Revision history

Version	Date	Change
1.0	10-May-2023	Initial Version

23. Appendix 1: Programming Conventions for Tables, Data Listings and Figures (TLFs)

23.1 Paper Size, Orientation and Margins

The margin, page size and line size specifications as stipulated in Table 23.1 will be used for the presentation of all TLFs.

Table 23.1: Output margin, page size and line size specifications

	Landscape	Portrait
Margins (Inches):		
Top	1.25	1
Bottom	1	1
Left	1	1.25
Right	1	1
Header (Inches)	0.5	0.5
Footer (Inches)	0.5	0.5
SAS® specifications:		
PAGESIZE	46	67
LINE SIZE	134	93

23.2 Fonts

The font type “Courier New” should be used as default for tables and data listings, with a font size of 8. The font color should be black. No bolding, underlining and italics are permitted.

Figures should have a default font of “Times Roman”, “Helvetica” or “Courier New”.

23.3 Header Information

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page).
- The sponsor name should appear in row 1, left-aligned.
- The word “CONFIDENTIAL” should appear in row 1, right-aligned.
- The protocol number should appear in row 2, left-aligned.
- The page identification in the format Page X of Y (where Y is the total number of pages for the TLF) should appear in row 2, right-aligned.
- The TLF identification number should appear in row 3, centered.
- The TLF title should start in row 4, centered.

- The TLF population should appear in row 5, centered. The population should be spelled out in full, e.g. Safety analysis population in preference to Safety analysis population.
- Row 6 should be a continuous row of underscores ('_') (the number of underscores should equal the line size).
- Row 7 should be a blank line.
- Mixed case should be used for titles.
- Titles should not contain quotation marks or footnote references.
- The column headings should be underlined with a row of underscores ('_').
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered.
- Column headings containing numbers should be centered.
- Column headings should be in mixed case.
- In general, the analysis population count should appear in the column header in the form "(N=XX)".

23.4 Table and Data Listing Table, Listing and Figure (TLF) Conventions

23.4.1 General

- The first row in the body of the table or data listing should be blank.
- The left-hand column should start in Column 1. No indenting or centering of the TLF should occur.
- Rounding should be done with the SAS® function ROUND.
- Numerical values in tables should be rounded, not truncated.
- Numerical values should be decimal point aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- The study drug should appear first in tables with treatment group as columns.
- All variables contained on the eCRF (which have data present) should appear in the data listings, along with all derived data appearing in the corresponding tables.
- The width of the TLF should match the line size.

23.4.2 Univariate statistics

- Statistics should be presented in the same order across tables (i.e., n, mean, SD, minimum, median and maximum).

- If the original data has N decimal places, then the summary statistics should have the following decimal places:
    - Minimum, maximum and CV (%): N
    - Mean and median: N + 1.
    - SD: N + 2.

23.4.3 Frequencies and percentages [n, (m) and %]

- Mentions should be reported inside parentheses, with one space between the count and the left parenthesis of the mentions. An example is given below:
    - 124 (645)
- Percent values should be reported inside parentheses, with one space between the right parenthesis of the mention and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
    - 77 (156) (100.0)
    - 50 (56) (64.9)
    - 0 (0) (0.0)
- Percentages will be reported to one decimal place, except percentages <100.0 but >99.9 will be presented as '>99.9' (e.g., 99.99 is presented as >99.9); and percentages <0.1 will be presented as '<0.1' (e.g., 0.08 is presented as <0.1). Rounding will be applied after the <0.1 and >99.9 rule.
    - (<0.1)
    - (6.8)
    - (>99.9)

- Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
- Where counts are zero, mentions of 0 and percentages of 0.0 should appear in the table.

23.4.4 Confidence intervals (CIs)

- CIs should be presented with one additional decimal place as that of the raw data, and SDs and standard errors (SEs) with two additional decimal places as that of the raw data.

- CIs should be justified so that parentheses displayed on consecutive lines of a table “line up”.

23.4.5 P-values

- P-values should be reported to four decimal places. If p-value is 0.0000 then we present it <0.0001 and p-value is 1.0000 then it >0.9999.

23.4.6 Ratios

- Ratios should be reported with one additional decimal place as that of the raw data.

23.4.7 Spacing

- There should be a minimum of 1 blank space between columns (preferably 2).

23.4.8 Missing values

- A “0” should be used to indicate a zero frequency.
- A blank will be used to indicate missing data in data listings.

23.5 Figure output conventions

Figures should be provided in RTF files using the SAS® Output Delivery System (ODS).

23.6 Dates and times

Depending on data available, dates and times will take the form ddMMMyyyy and hh:mm.

23.7 Spelling format

The spelling format to be used is English US.

23.8 Presentation of treatment groups

Treatment:

- Brolucizumab

23.9 Presentation of visits

- Visit 1 (Week 0)
- Visit 2 (Week 4
- Visit 3 (Week 8)
- Visit 4 (Week 16)
- Visit 5 (Week 20)
- Visit 6 (Week 24)
- Visit 7 (Week 32)

- Visit 8 (Week 40)
- Visit 9 (Week 44)
- Visit 10 (Week 48)
- Visit 11 (Week 56)

24. Appendix 2: Partial date conventions and Concomitant medication guidelines

The whole missing date will not be imputed for this study; only partial date imputation will be performed. Conventions pertaining to partial dates are presented.

24.1 Table: Algorithm for partial date imputation for Concomitant Mediation (CM)

Concomitant Medication	Missing	Imputation
Start Date	Day	If CM start Month = Treatment start month and CM start Year = Treatment start Year, then CM start Day= minimum of (Treatment Start Day or CM end Day). Otherwise CM start day = “01”.
	Day and Month	If CM start Year = Treatment start Year, then CM start Day and Month = minimum of (Treatment Start Day and Month or CM end Day and Month). Otherwise CM start Day and Month = “01 Jan”.
	Day, Month and Year	No Imputation will be performed.
End Date	Day	If CM End Month = Study conclusion Month and CM End Year= Study conclusion Year, Then CM End Day= Study Conclusion Day. Otherwise CM End Day = last day of respective month.
	Day and Month	If CM End Year = Study Conclusion Year, then CM End Day and Month = Study Conclusion Day and Month. Otherwise CM End Day and Month = “31 Dec”.
	Day, Month and Year	No Imputation will be performed.

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Envelope Sent	Hashed/Encrypted	15-May-2023 | 06:00
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Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
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