NOVARTIS

Clinical Development

RTH258/Brolucizumab

CRTH258D2301 / NCT04278417

A 96-week, two-arm, randomized, single-masked, multi-center, phase III study assessing the efficacy and safety of brolucizumab 6 mg compared to panretinal photocoagulation laser in patients with proliferative diabetic retinopathy (CONDOR)

Statistical Analysis Plan (SAP)

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16-Dec-2020	Prior to start of any statistical programming work	Creation of first final version	N/A - First final version	
31-Aug-2023	Prior to start of any statistical programming work	Creation of amendment 1	Add analysis timing for event data in the primary analysis	Sections 2.1, 2.13
			Add analyses to cover potential impact of COVID-19	Sections 2.3.1, 5.6
			Add summary table for laboratory data, as per the protocol	Sections 2.8.3, 5.3
			Add summary table for post-treatment deaths, as per the protocol	Section 2.8.2
			Correct minor issues in the first version	Sections 1, 2.2.1, 2.3.1, 2.3.3, 2.4.1, 2.4.2, 2.5.2, 2.6.1.1, 2.7.1.1, 2.8.1.2, 2.10.1
			Add cut-off logic for the primary analysis at Week 54	Section 2.1
			Update end of study day mapping and end of treatment day mapping	Section 2.1.1

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Update rule of exclusion criteria of analysis sets	Section 5.5
			Update definitions of impacted and non-impacted subjects due to COVID-19	Section 5.6
			Update approach to handle censored/missing data	Sections 2.6.3, 2.8.3, 2.8.4, 2.10.1, 2.10.2, 2.10.3, 2.12.2
			Add additional secondary endpoint to testing strategy	Sections 2.6.2, 2.7.2.1
			Add analyses for discontinuation	Sections 2.3.2, 2.5.4, 2.6.4, 2.7.4, 2.8.1
			Update statistical models	Section 5.4
			Add sensitivity analysis for the first key secondary endpoint	Section 2.6.4.1
			Update changes to protocol specified analyses	Section 4
			Unify the wording for alternative treatment as “alternative DR treatment / relevant DME treatment”	Whenever applicable
			Update definitions of ocular complications	Sections 2.7.1.2, 2.7.3
			Add subgroup defined on baseline CSFT	Sections 2.2.1, 2.3.2, 2.6.4

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Include vitrectomy to the list of alternative treatments	Section 2.1.1
17-Nov-2023	Prior to DBL	Creation of amendment 2	Add description for alternative treatment	Sections 2.1.1
			Update the categories for DRSS	Section 2.2, 2.3,2.5,2.6
			Change the two-sided p value to one-sided	Section 2.5.2
			Provide detailed analysis part for additional analyses	Section 2.5.4, 2.6.4
			Report BCVA >= 84 at each scheduled visit	Section 2.7.4
			Simplify the analysis for DR status over time	Section 2.7.4
			[redacted]	[redacted]

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List of abbreviations

AE	Adverse event
AESI	Adverse events of special interest
AR	Analysis restriction
ANCOVA	Analysis of covariance
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
BCVA	Best corrected visual acuity
CFP	Color fundus photography
CI	Confidence interval
CI-DME	Center-involved diabetic macular edema
CM	Concomitant medication
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease-2019
CRC	Central reading center
CSFT	Central subfield thickness
CSR	Clinical study report
DBL	Database lock
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRSS	Diabetic retinopathy severity scale
eCRS	Electronic case retrieval strategy
EOS	End of study
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
GLMM	Generalized Linear Mixed Model
HbA1c	Glycosylated hemoglobin A1c
IOP	Intraocular pressure
IRF	Intraretinal fluid
KM	Kaplan-Meier
LOCF	Last observation carried forward
LSM	Least squares mean
MAR	Missing At Random
MedDRA	Medical Dictionary for Drug Regulatory Activities
MICE	Multiple imputation by chained equations
MMRM	Mixed Model for Repeated Measures
NPDR	Non-proliferative diabetic retinopathy
OCT	Optical coherent tomography
[redacted]	[redacted]
PD	Protocol deviation
PDR	Proliferative diabetic retinopathy
PDS	Programming dataset specification
[redacted]	[redacted]
PPS	Per-protocol set

[redacted]	[redacted]
PRP	Panretinal photocoagulation
PT	Preferred term
q12w	Every 12 weeks
q6w	Every 6 weeks
[redacted]	[redacted]
SAE	Severe adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
SRF	Subretinal fluid
TEAE	Treatment-emergent adverse event
TRD	Technical research and development
VEGF	Vascular endothelial growth factor
[redacted]	[redacted]
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of statistical analyses planned in the study protocol, and to provide detailed statistical methods that will be used for the Clinical Study Report (CSR) of study CRTH258D2301.

The analyses will be conducted at two time points as described below:

- The interim analysis (IA), which is also the primary analysis, will be conducted at Week 54 once all initially planned number of subjects have completed the Week 54 visit or discontinued the study prior to Week 54.
- The final analysis will be conducted at Week 96 once all subjects have completed or discontinued the study.

An interim CSR and a final CSR will be provided.

Data will be analyzed according to the analysis plan specified in this document which will be incorporated into Section 9.7 and Appendix 16.1.9 of the CSR.

The SAP may be amended if needed before the first database lock (DBL) for the primary analysis at Week 54. Any changes to the SAP after approval will be documented. The following document was referenced while writing this SAP:

CRTH258D2301 Clinical Trial Protocol Amended version 02 dated 28-Sep-2021.

1.1 Study design

The study is a 96-week, two-arm, randomized, single-masked, multi-center, active-controlled, non-inferiority study in subjects with proliferative diabetic retinopathy (PDR).

Subjects who consent will undergo screening assessments to evaluate their eligibility based on the inclusion and exclusion criteria. Subjects who meet all the inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio to one of the following treatments (see Figure 1-1):

- Brolucizumab 6 mg: 3 x q6w loading then q12w maintenance through Week 90, with the option from Week 48 onwards to extend the treatment interval by 6 weeks at a time up to 24 weeks.
- Panretinal photocoagulation (PRP): initial treatment in 1-4 sessions up to Week 12, followed with additional PRP treatment (may split into 2-4 sessions) as needed up to Week 90.

The randomization will be stratified by region.

Visits will occur every 6 weeks throughout the study, regardless of whether the subject receives treatment or not.

Approximately 706 subjects (353 per arm, 15% dropout rate expected) will be randomized. The maximum study duration for one subject is 99 weeks, including Screening and post-treatment follow-up.

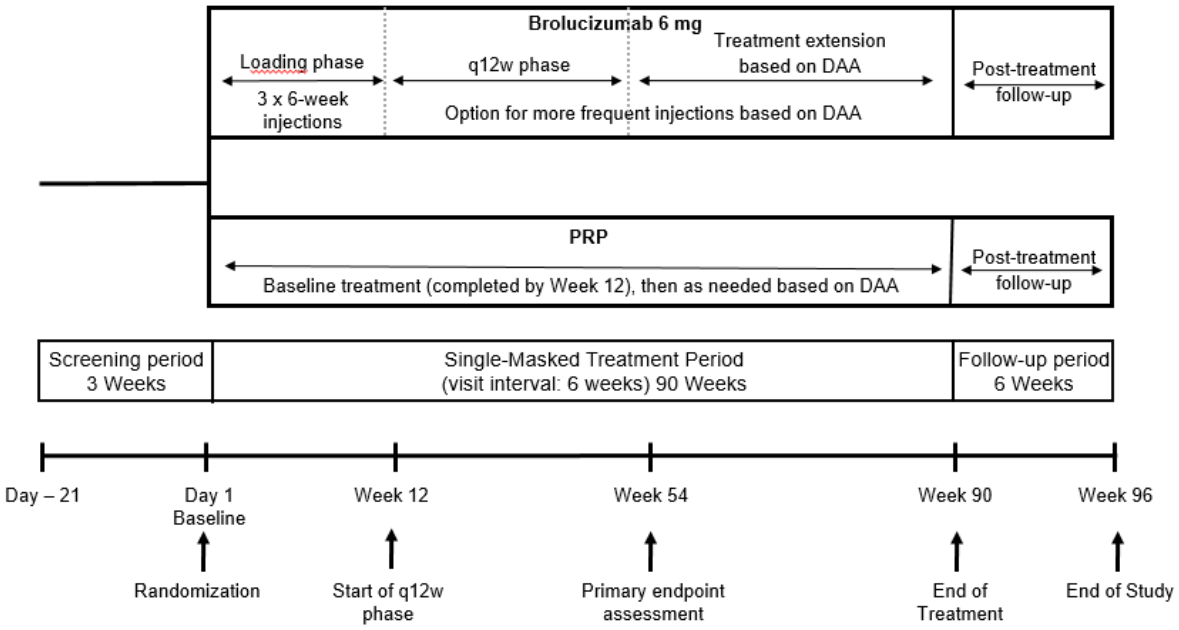
There will be 3 periods in this study (see Figure 1-1):

- Screening period: from Day -21 to Baseline (Day 1)

- Single-masked treatment period: from Baseline (Day 1) to Week 90 (End-of-Treatment)
- Post-treatment follow-up period: from Week 90 to Week 96 (End-of-Study)

Further details can be found in the study protocol.

Figure 1-1 Study design



DAA: Disease activity assessment

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that brolucizumab is non-inferior to PRP with respect to the change from Baseline in visual acuity at Week 54	• Change from Baseline in best corrected visual acuity (BCVA) at Week 54
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To demonstrate that brolucizumab is superior to PRP in reducing diabetic retinopathy (DR) severity at Week 54	• Proportion of subjects with no PDR at Week 54
• To demonstrate that brolucizumab is superior to PRP in preventing the development of center-involved diabetic macular edema (CI-DME) up to Week 54	• Proportion of subjects with CI-DME up to Week 54
• To compare the effect of brolucizumab relative to PRP with respect to visual acuity	• Area under the curve (AUC) in change from Baseline in BCVA up to Week 54 and Week 96

Objective(s)	Endpoint(s)
• To compare the effect of brolucizumab relative to PRP on DR status	• Step-change from Baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) at Week 54 and Week 96 • Proportion of subjects with no PDR at Week 96
• To compare the effect of brolucizumab relative to PRP on ocular complications	• Proportion of study eyes developing vision-threatening complications associated with DR up to Week 54 and Week 96 • Proportion of subjects with CI-DME up to Week 96
• To assess the safety and tolerability of brolucizumab relative to PRP	• Incidence of ocular and non-ocular adverse events (AEs) up to Week 54 and Week 96

[redacted]

2 Statistical methods

2.1 Data analysis general information

The clinical database including all Week 54 data will be freezed once all initially planned number of subjects have completed the Week 54 visit or discontinued the study prior to Week 54. The primary analysis based on Week 54 data will be derived from this database. For event-

driven analyses (e.g., time-to-event endpoints and AEs), Week 54 cut-off date will be derived at subject level. Only events occurred prior to or on the cut-off date (e.g., AE start date ≤ cut-off date) will be included in the primary analyses. For screen failures and subjects discontinued study prior to or on Week 54 (with a study disposition day < 414), include all data collected for all domains. Otherwise refer to the cut-off rules below.

For date-based domains, derive cut-off date at subject level according to the logic provided below and include only the records in each dataset occurred prior to or on the cut-off date.

- If a subject attended Week 54 visit, then cut-off date = visit end date of Week 54 visit.
- If a subject skipped Week 54 visit but has a last attended scheduled visit after Week 54 or discontinued after Week 54 (study disposition day ≥ 414), cut-off date = Day 1 + 412.

For visit-based domains, scheduled and unscheduled visits up to Week 54 will be included; early exist visits after Week 54 or with a visit day ≥ 414 will be excluded.

For protocol deviations, the study visit rules will be applied to records collected based on visits and the cut-off date rules will be applied to other records.

All subjects still in the study beyond Week 54 will continue to receive study treatment as scheduled through the planned study duration. The analysis of the data collected after the Week 54 visit will be performed once all subjects complete the end of study (EOS) visit or discontinue from the study.

The statistical analysis will be performed by Novartis using SAS Version 9.4 or above.

Summary statistics will be presented by treatment arm unless otherwise specified. For continuous variables, summary statistics will generally include the number of observations, mean, standard deviation, median, quartiles, minimum and maximum. For categorical variables, these will generally include the number of observations, the number of observations in each category and the corresponding percentage. For treatment comparison between brolucizumab and PRP, point estimates and 95% CIs will be provided as appropriate unless otherwise specified.

All the analyses listed in the SAP that correspond to data collected during the 2nd year of the study (post-Week 54) will be part of the end of study (year-2; final) CSR only. For the year-2 CSR, efficacy endpoints specific to the first year, i.e., up to the Week 54 visit (e.g., the change from Baseline in BCVA at Week 54) will not be analyzed and reported again; analyses by visit and assessments based on cumulative data (e.g., incidence of AEs) will include data from Baseline up to the end of study.

2.1.1 General definitions

Study treatment

Study treatment refers to both brolucizumab 6mg injections and PRP.

Study day

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

Therefore, for a particular date, study day will be calculated as follows:

- For dates on or after the date of first administration of study treatment:

  Study day = Assessment date – Date of first dose of study treatment + 1.

- For dates prior to the date of first administration of study treatment:

  Study day = Assessment date – Date of first dose of study treatment.

Baseline

The baseline value is defined as the last assessment performed prior to administration of the first dose of study treatment.

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

End of study day mapping

The end of study (EOS) date is the date when a subject completed or discontinued the study, whichever occurs first.

For reporting data by visit in outputs, the EOS visit will be allocated to the actual (reported) visit number. If EOS date is not on a scheduled visit, then the EOS visit will be allocated based on study day, to the closest future scheduled study visit. For example, if EOS date is not on a scheduled visit and the subject attended the previous scheduled visit, then EOS date will be allocated to the next scheduled visit; if the EOS date is not on a scheduled visit and the subject missed the previous scheduled visit, then EOS date will be allocated to the previous scheduled visit.

End of treatment day mapping

The end of treatment (EOT) date is the date when a subject completed or discontinued the study treatment, whichever occurs first. The “Date of Last Exposure” is the date of the last study treatment on or prior to the EOT date.

For reporting data by visit in outputs, the EOT visit will be allocated to the actual (reported) visit number. If EOT date is not on a scheduled visit, then the EOT visit will be allocated based on study day, to the closest future scheduled study visit.

Unscheduled visits

Data collected at unscheduled visits will not be used in ‘by-visit’ tabulations or graphs but will be included in analyses based on all post-baseline values such as last observation carried forward (LOCF) imputation.

All data collected at unscheduled visits will be included in listings.

Missing and implausible dates

The general approach to handling missing dates is shown in Section 5.1.

Alternative DR treatment / relevant DME treatment

Medications/procedures for diabetic retinopathy (DR) other than the assigned study treatments, or medications/procedures for DME in the study eye after first dose of study treatment which may have an impact on the interpretation of the results for the primary and key secondary estimands are listed in Table 2-1.

Table 2-1 Alternative DR treatment / relevant DME treatment

Alternative DR treatment / relevant DME treatment	Endpoints impacted
Anti-VEGF therapy other than assigned study treatment	BCVA, DRSS, Center-involved DME (CI-DME)
PRP other than assigned study treatment	BCVA, DRSS
Periocular injection or intraocular administration of corticosteroids	BCVA, CI-DME, DRSS
Grid/focal laser photocoagulation	BCVA, CI-DME
Vitrectomy for DR complications	BCVA, DRSS*

*: it is assumed that the impact of vitrectomy on DRSS is limited if the data is collected after 3 months from the procedure.

The specific impact to each endpoint is discussed in the corresponding analysis sections.

Censored data

Censored data refers to data that are excluded from analysis after occurrence of specific intercurrent events (e.g., use of alternative DR treatment / relevant DME treatment).

To be noted that the above definition mainly applies for variables not using time-to-event analysis. In time-to-event analysis, censoring may also happen for administrative reason other than intercurrent events (e.g., in a Kaplan-Meier analysis, subjects without the event of interest may be censored at the date of data cut-off).

Missing data

Missing data refers to data that should be collected but are not collected due to reasons other than intercurrent events, e.g., subject is lost to follow up.

2.2 Analysis sets

The **All Enrolled Set** includes all subjects who have signed informed consent and are assigned subject numbers.

The **Randomized Set** will consist of all randomized subjects. Subjects are considered randomized when they have been deemed eligible for randomization by the investigator and given a randomization number. Subjects who were randomized but did not receive any study treatment at baseline and discontinued study per subject decision will be classified as screen failures. Subjects will be analyzed according to the treatment assigned to them at randomization.

The **Full Analysis Set** (FAS) comprises all randomized subjects who receive at least one study treatment. Subjects in the FAS will be analyzed according to the treatment assigned to them at randomization.

The **Safety Analysis Set** (SAF) includes all subjects who receive at least one study treatment. Subjects in the SAF will be analyzed according to the actual study treatment they

received, where treatment received is defined as the randomized/assigned treatment if the subject took at least one dose of that treatment, or the first treatment received if the randomized/assigned treatment was never received.

Supportive analyses of the primary endpoint will include analyses using the **Per Protocol Set** (PPS). PPS is a subset of the FAS and will exclude or censor data from subjects with important protocol deviations (PDs) and analysis restrictions (ARs) that are expected to majorly affect the validity of the assessment of efficacy at Week 54.

Prior to locking the database for the primary analysis at Week 54, the relevant important PDs will be identified as specified in Section 5.5. The corresponding identifications at the subject level, including data exclusion from PPS and censoring, will be captured in the database. ARs (i.e., non-protocol deviations) will be identified by programming (as specified in the programming specification document) independently to the treatment arm.

Rules of exclusion criteria of analysis sets are described in Section 5.5.

2.2.1 Subgroups of interest

The subgroups of interest are specified below:

- Age category (<55, ≥55 years)
- Sex (male, female)
- Baseline BCVA categories (≤75, >75 letters)
- Diabetes type (Type 1, Type 2)
- Baseline glycosylated hemoglobin A1c (HbA1c) categories (<7.5, ≥7.5%)
- Baseline DR severity categories (NPDR, Mild or moderate PDR, High-risk PDR or worse, Ungradable) as assessed by Central Reading Center (CRC)
- Region (US and Canada, East Asia [Japan, Taiwan, South Korea, Philippines, China], Other).
- Prior anti-VEGF treatment in the study eye (yes, no)
- Baseline CSFT (<280, ≥280 µm) as assessed by CRC

Subgroup analyses will be performed for the primary efficacy variable using FAS and the primary analysis approach, if there are sufficient number of patients in each subgroup to allow model convergence and yield valid interpretation of the subgroup analyses. More details can be found in Section 2.5.4.

To support local regulatory requirements, analysis of key efficacy and safety data (e.g., primary endpoint, key secondary endpoints, adverse events, disposition, demographics and exposure) for the subgroup of subjects from a specific country, e.g., Japan, China, may be performed and provided in separate reports.

2.3 Subject disposition, demographics and other baseline characteristics

2.3.1 Subject disposition

The following summaries will be included in the disposition table considering all enrolled subjects (all enrolled set): the number and percentage of subjects who were enrolled into the

study, treated, completed a specific study period (Week 54/Week 96), discontinued the study (prior to or at Week 54/Week 96) (including reasons for study discontinuation) and discontinued from study treatment (prior to or at Week 54/Week 96) (including reasons for study treatment discontinuation). For disposition table up to Week 54, the number and percentage of ongoing subjects will also be provided.

The number and percentage of subjects who discontinued study and who discontinued study treatment will be presented by study visit. The number and percentage of subjects treated by country and site will be presented. These outputs will be based on the randomized set.

A listing of subjects who discontinued study earlier than the planned EOS will be provided by treatment arm using the randomized set. A separate listing will be provided for subjects who discontinued study treatment earlier than the planned EOT. Each listing will identify the last visit completed and when the study or study treatment was discontinued including the corresponding reason.

Subjects who signed an informed consent form and who were subsequently found to be ineligible prior to randomization will be considered a screen failure. A by-subject listing of reasons for screen failure will be presented using the all enrolled set. The number and percentage of subjects with important PDs will be presented by treatment arm and deviation category. The number and percentage of subjects with PDs that occurred related to COVID-19 will also be provided by deviation category and treatment arm. In addition, the number and percentage of subject with important PDs and ARs leading to exclusion from analysis sets will be provided by treatment arm and deviation/restriction category. Important PDs and ARs will be listed separately. These outputs are based on the randomized set.

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

2.3.2 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics for the FAS by treatment arm and overall. Demographic characteristics will include age, gender, race, ethnicity and region. Demographics and baseline characteristics by subgroup of COVID-19 impact will also be provided.

Summary statistics will be presented for the study eye if they are baseline ocular characteristics. Listings will be presented separately for the study eye and the fellow eye.

Baseline characteristics include:

- Study eye selection (left eye or right eye)
- Diabetes type (Type 1, Type 2)
- Duration of diabetes since the primary diagnosis
- Baseline BCVA as continuous variable and using categories (≤75, >75 letters, and ≤70, >70-<80, ≥80 letters)
- Baseline HbA1c as continuous variable and using categories (<7.5, ≥7.5%)
- Baseline CSFT as assessed by CRC as continuous variable and using categories (<280, ≥280 μm)

- Baseline DR severity categories (NPDR, Mild or moderate PDR, High-risk PDR or worse, Ungradable) and ETDRS DRSS using 12-level scale (see Table 2-3) as assessed by CRC
- Baseline status of intraretinal fluid (IRF) (presence, absence) as assessed by CRC
- Baseline status of subretinal fluid (SRF) (presence, absence) as assessed by CRC

Duration of diabetes since diagnosis (months) will be derived as [(first dose date – diagnosis start date + 1)/365.25*12]. In case of partial dates, the imputation rule is specified in Section 5.1.4.

Other relevant baseline information will be summarized with descriptive statistics and listed as appropriate.

No tests for differences in demographics and baseline characteristics between treatment arms will be performed. Potential differences will be assessed based on clinical relevance.

If the number of discontinuations crossed the quality tolerance limit (15% for study treatment discontinuation and 5% for study discontinuation), demographics and baseline characteristics will also be summarized by subject status (i.e., discontinued versus not discontinued study treatment, discontinued versus not discontinued study up to Week 54).

2.3.3 Medical history

Medical history and current medical conditions will be summarized and listed for ocular (study eye) and non-ocular events. [redacted]

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

2.4.1 Study treatment / compliance

For brolucizumab group, extent of exposure to study treatment is calculated as the number of brolucizumab injections received. For PRP group, extent of exposure to study treatment is calculated as the number of PRP treatments performed.

Descriptive statistics for exposure to study treatment will be provided for the SAF.

The following summaries will be presented separately for the brolucizumab arm and the PRP arm:

- Overall number of treatments: for the brolucizumab arm, the number of treatments will be summarized cumulatively by time period, including the loading phase (Baseline to Week 12), the maintenance phase (Week 18 to Week 54/Week 90), and the overall period (Baseline to Week 54/Week 90). For the PRP arm, the number of treatments and the number of sessions will be presented separately for subjects who only received baseline PRP treatment and subjects who received at least one additional PRP treatment besides the baseline treatment.
- Treatment exposure by visit: the number and proportion of subjects who received study treatments and missed visits will be presented by treatment arm and visit.

[redacted]

2.4.2 Prior and concomitant therapies

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Concomitant medications are defined as medications received after the start of study treatment including those already started prior to the start of the study treatment.

Prior and concomitant medications will be coded according to the WHO Drug Reference List dictionary with Anatomical Therapeutic Classification (ATC) class and preferred term (PT).

Ocular and non-ocular prior and concomitant medications will be summarized and listed by ATC class and PT by treatment arm. Ocular medications prior to start of study treatment will be listed for the study eye and the fellow eye separately. Non-ocular medications prior to start of study treatment will also be listed by treatment arm.

Anti-VEGF medications will be summarized by ATC class and PT for systemic route, the study eye and the fellow eye separately by treatment arm.

Ocular concomitant non-drug therapies and procedures will be summarized for the study eye only. Both ocular and non-ocular concomitant non-drug therapies and procedures will be listed.

In the summary tables mentioned above, data collected after the start of alternative DR treatment / relevant DME treatment in the study eye will be censored (from the day the subject started alternative DR treatment / relevant DME treatment onwards).

Alternative DR treatment / relevant DME treatment in the study eye as mentioned in Table 2-1 will be summarized by treatment arm, for overall and each category. A listing of subjects who received alternative DR treatment / relevant DME treatment in the study eye will be provided.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary endpoint is the change from Baseline in BCVA at Week 54. This endpoint is defined with respect to the study eye.

2.5.2 Statistical hypothesis, model, and method of analysis

The objective related to the primary endpoint is to demonstrate non-inferiority of brolucizumab versus PRP with respect to the change from Baseline in BCVA at Week 54, assuming a non-inferiority margin of 4 ETDRS letters.

Let:

B = Brolucizumab 6 mg

P = PRP

Consider the following non-inferiority hypotheses related to a non-inferiority margin of 4 letters:

H_{01}: $\mu_B - \mu_P \leq -4$ letters versus H_{A1}: $\mu_B - \mu_P > -4$ letters

where μ_B and μ_P are the corresponding unknown true mean changes from Baseline in BCVA at Week 54 in the brolucizumab and PRP arms, respectively.

The primary estimand associated with the above hypotheses is defined as the between-treatment difference in change from Baseline in BCVA at Week 54, excluding the confounding effect of alternative DR treatment / relevant DME treatment (see Table 2-1) applied to the study eye. The analysis set for the primary estimand will be the FAS as described in Table 2-2.

Based on the FAS, the above hypotheses will be tested via an analysis of covariance (ANCOVA) model. The model will include treatment, baseline DR Severity category (NPDR, Mild or moderate PDR, High-risk PDR or worse, Ungradable), age category (< 55, ≥ 55) and region (US and Canada, East Asia, Other) as factors, and baseline BCVA as a covariate.

A two-sided 95% confidence interval (CI) for the least squares mean (LSM) difference (brolucizumab - PRP) at Week 54 will be presented in letters. Non-inferiority will be considered established if the lower limit of the corresponding 95% CI is greater than -4 letters. P-value for treatment comparison (one-sided) and p-value for non-inferiority (4 letter margin) (one-sided) will be presented.

The following superiority hypotheses for the primary endpoint may be further evaluated after non-inferiority for the primary endpoint and superiority for the proportion of subjects with no PDR are established:

H_{02}: $\mu_B - \mu_P \leq 0$ letters versus H_{A2}: $\mu_B - \mu_P > 0$ letters.

Superiority in BCVA will be considered established if the lower limit of the corresponding 95% CI from the same ANCOVA model used to assess for non-inferiority analysis is greater than 0 letters.

Multiplicity control for hypothesis testing based on the primary endpoint and key secondary endpoints is discussed in Section 2.6.2.3.

2.5.3 Handling of missing values/censoring/discontinuations

The primary estimand and other supplementary estimands of interest are noted in Table 2-2 below together with their key attributes, including the handling of intercurrent events associated with the use of alternative treatment(s) for DR or treatment(s) of DME in the study eye.

Table 2-2 Primary and its supplementary estimands

Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (including missing data strategy)
Primary estimand	Difference in change from Baseline in BCVA at Week 54 excluding the effect of alternative DR treatment(s) / relevant DME treatment(s)	FAS	All data captured until the start of alternative DR treatment(s) / relevant DME treatment(s) will be included	ANCOVA model as specified in Section 2.5.2; last observation carried forward (LOCF) imputation / replacement for missing data /censored data

Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (including missing data strategy)
Supplementary estimand A0	Difference in change from Baseline in BCVA at Week 54 regardless of alternative DR treatment(s) / relevant DME treatment(s)	FAS	All data captured will be included	ANCOVA model as per the primary estimand; LOCF imputation for missing data
Supplementary estimand B0	Difference in change from Baseline in BCVA at Week 54 excluding the effect of alternative DR treatment(s) / relevant DME treatment(s) and important PDs/ARs as per the definition of the PPS	PPS	All data captured until the start of alternative DR treatment(s) / relevant DME treatment(s) or relevant PDs/ARs will be included	ANCOVA model as per the primary estimand; LOCF imputation / replacement for missing /censored data

Handling of intercurrent events

Use of alternative DR treatment / relevant DME treatment (see Table 2-1) in the study eye is considered as the important intercurrent event for the primary estimand, taking into account that those treatments can potentially improve the vision, thus confound the treatment effect of interest and lead to a conclusion that favors the inferior treatment.

For subjects who received alternative DR treatment / relevant DME treatment in the study eye before Week 54, the data collected after this event will be censored and BCVA values at Week 54 will be replaced by their last observation prior to this event.

Handling of missing values not related to intercurrent event

Missing BCVA values will be imputed by LOCF as a primary approach. Observed values from both scheduled and unscheduled visits will be used for the LOCF imputation. For subjects with no post-Baseline BCVA value, the baseline value will be carried forward.

LOCF is an established method within the assessment of efficacy of anti-VEGF treatments in terms of BCVA outcome. In case of missing data occurring independently of the response to study treatment, the LOCF approach assumes stability which seems to be adequate based on the nature of the disease progression and historical data. In case of missing data due to lack of efficacy or safety/tolerability with impairment of the function of the study eye, the LOCF method would be able to capture such an unfavorable outcome as reflected in the last observed measurement.

2.5.4 Supportive analyses

Sensitivity analyses

For the primary estimand, to assess the robustness of the results to the assumptions for the data handling approach mentioned above, sensitivity analyses using alternative methods of handling missing or confounded data other than LOCF will be performed.

A multiple imputation by chained equations (MICE) method will be used in the sensitivity analysis. Regression models including the same factors/covariate in the primary ANCOVA model and BCVA values at each visit will be used for the imputation. BCVA values collected after start of alternative DR treatment / relevant DME treatment are not included in the imputation model.

Supplementary analyses related to supplementary estimands are mentioned in Table 2-2.

The supplementary analysis for supportive estimand A0 will also include data after use alternative DR treatment / relevant DME treatments.

The supplementary analysis for supportive estimand B0 will be provided when there are more than 10% of subjects with important PD/AR mentioned in Section 5.5.

In addition to the sensitivity analyses and supplementary analyses mentioned above, other supportive analyses are specified below.

Subgroup analyses will be conducted to assess the consistency of treatment effect across various subgroups of interest as described in Section 2.2.1. They will be conducted using the framework for the primary estimand only (FAS with censoring of data collected after use of alternative DR treatment / relevant DME treatment in the study eye, and missing/censored values imputed/replaced using LOCF):

- Subgroup analyses will be conducted using the same model and analysis strategies described for the primary endpoint but fitted by category of each of the subgroups. Subgroup variables that are used as fixed effects in the model will be removed from the model statement for the subgroup analysis.
- In case of analyses on subgroups with extremely imbalanced sample sizes, the subgroup levels can either be combined, if appropriate, or the extremely small subgroup will be excluded while fitting the analysis model.
- Subgroup analysis results will be presented using forest plots.

Additional subgroup analysis will be performed to evaluate the impact of COVID-19 pandemic.

If the number of discontinuations crossed the quality tolerance limit (see Section 2.3.2), **additional analyses** will be conducted to evaluate the impact of discontinuation:

- Change from baseline in BCVA with error bars representing ± standard error (SE) will be presented by visit and by treatment group using line plots. Separate plots will be provided for subjects who discontinued versus not discontinued study treatment and for subjects who discontinued versus not discontinued study. This will be conducted using the same framework of the primary estimand (FAS with censoring of data collected after use of alternative DR treatment/relevant DME treatment in the study eye, and missing/censored values imputed/replaced using LOCF).
- Evaluate the treatment effect using a hypothetical strategy with the following attributes:

  Population: subjects with PDR (i.e., the entire study population)

Endpoint: change from baseline in BCVA at Week 54

Treatment: brolucizumab 6 mg/PRP

Intercurrent events: use of alternative DR treatment / relevant DME treatment, which will be handled by LOCF as described in Section 2.5.3; study treatment discontinuation, which will be handled by the prediction of hypothetical trajectories, assuming treatment discontinuation had not occurred and subjects who discontinued would behave similarly as those who did not on the same treatment arm. If both intercurrent events occurred to the same subject, data will be handled according to the first event

Summary measure: difference in means for change from baseline in BCVA

The hypothetical estimand will be analyzed using the mixed model for repeated measures (MMRM) with missing at random (MAR) assumption. The model will include treatment, visit, baseline BCVA, baseline DR Severity category (NPDR, Mild or moderate PDR, High-risk PDR or worse, Ungradable), age category (< 55, ≥ 55), region (US and Canada, East Asia, Other) and treatment by visit interaction as fixed-effect terms and visit as a repeated measure. An unstructured covariance matrix will be used to model the within-subject error. If the MMRM with an unstructured covariance matrix does not converge, a more restricted covariance matrix can be considered in the following order until convergence is reached: Toeplitz, first-order autoregressive, compound symmetry and variance components. Treatment difference (brolucizumab - PRP) at Week 54 will be estimated using the LSM and 95% CI.

Given reasonable assumption(s) (e.g., principal ignorability), additional analysis may be performed to evaluate the treatment effect on the principal stratum of subjects who would not discontinue treatment regardless of treatment assignment.

2.6 Analysis of the key secondary objectives

2.6.1 Key secondary endpoints

The key secondary endpoints are defined with respect to the study eye.

2.6.1.1 PDR status at Week 54

The first key secondary endpoint is the proportion of subjects with no PDR in the study eye at Week 54. This endpoint will be derived from the DRSS assessed by the CRC using 7-field color fundus photography (CFP) images. The DRSS values on the original scale are defined in Table 2-3 (first two columns from the left).

Table 2-3 Definition of DRSS: original scale and 12-level scale

Original scale	Definition	12-level scale	Definition
10	No retinopathy (DR absent)	1	DR absent
20	Very mild NPDR (Microaneurysms only)	2	Microaneurysms only
35	Mild non-proliferative diabetic retinopathy (NPDR)	3	Mild NPDR
43	Moderate NPDR	4	Moderate NPDR
47	Moderately severe NPDR	5	Moderately severe NPDR

Original scale	Definition	12-level scale	Definition
53	Severe NPDR	6	Severe NPDR
61	Mild PDR	7	Mild PDR
65	Moderate PDR	8	Moderate PDR
71	High-risk PDR	9	High-risk PDR
75	High-risk PDR	10	Very high-Risk PDR
81	Advanced PDR	11	Advanced PDR
85	Advanced PDR	12	Very advanced PDR

Other recorded DRSS values (code 98: Indeterminable due to missing images, code 99: Indeterminable due to ungradable images, code 00: No images received) that are not related to an evaluable DR severity level will be handled as missing. All DRSS values will be converted into a 12-level scale as defined in Table 2-3 (last two columns from the left). The event "no PDR" is defined as a DRSS < 61, or equivalently, DRSS (12-level scale) < 7.

2.6.1.2 Center-involved DME up to Week 54

The second key secondary endpoint is the proportion of subjects with CI-DME in the study eye up to Week 54. Subjects that have at least one CI-DME event in the study eye at any time point after Baseline will be classified as with CI-DME.

CI-DME is defined as CSFT ≥280 µm according to CRC evaluation of OCT image.

2.6.2 Statistical hypothesis, model, and method of analysis

2.6.2.1 PDR status at Week 54

The objective related to this key secondary endpoint is to demonstrate superiority of brolucizumab versus PRP with respect to increasing the proportion of subjects with no PDR at Week 54. The following hypotheses are defined:

H_{03}: $\pi_B - \pi_P \leq 0$ versus H_{A3}: $\pi_B - \pi_P > 0$

where π_B and π_P are the corresponding unknown true proportions of subjects with no PDR in the study eye at Week 54 in the brolucizumab and PRP arms, respectively.

The above hypotheses will be tested via Cochran-Mantel-Haenszel (CMH) test at a one-sided significance level of 0.025 using the FAS, after non-inferiority for the primary endpoint is established. Superiority will be considered established if the one-sided p-value from the CMH test is smaller than 0.025. The CMH test will include baseline DR Severity category (NPDR, Mild or moderate PDR, High-risk PDR or worse, Ungradable), age category (< 55, ≥ 55) and region (US and Canada, East Asia, Other) as adjusting factors. Multiplicity control is discussed in Section 2.6.2.3.

The difference in proportions between treatment arms will be estimated using the weighted average of the proportion differences over adjusting factors using the Mantel-Haenszel weights. Adjusting factors will be the same as for the CMH test. The corresponding 95% CI for the difference will be calculated based on normal approximation for binomial proportions. Details are provided in Section 5.4.

2.6.2.2 Center-involved DME up to Week 54

The objective related to this key secondary endpoint is to demonstrate superiority of brolucizumab versus PRP with respect to preventing the development of CI-DME up to Week 54. The following hypotheses are defined:

H_{04}: $\lambda_B - \lambda_P \geq 0$ versus H_{A4}: $\lambda_B - \lambda_P < 0$

where λ_B and λ_P are the corresponding unknown true proportions of subjects with at least one CI-DME event in the study eye up to Week 54 in the brolucizumab and PRP arms, respectively.

The above hypotheses will be tested via CMH test at a one-sided significance level of 0.025 using the FAS. Superiority will be considered established if the one-sided p-value from the CMH test is smaller than 0.025. The CMH test will include the same adjusting factors as for the first key secondary endpoint described in Section 2.6.2.1. Multiplicity control is discussed later in Section 2.6.2.3.

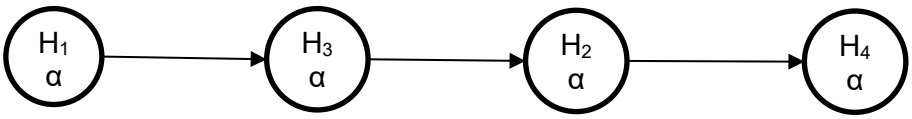
The difference in proportions between treatment arms will be estimated using the weighted average of the proportion differences over adjusting factors using the Mantel-Haenszel weights. Adjusting factors will be the same as for the CMH test. The corresponding 95% CI for the difference will be calculated based on normal approximation for binomial proportions. Details are provided in Section 5.4.

2.6.2.3 Multiplicity control of primary and key secondary endpoints

To control the overall type I error rate at a one-sided 0.025 level, testing of non-inferiority for the primary endpoint, superiority for the primary endpoint and superiority for the key secondary endpoints will be conducted in a hierarchical sequence as described below:

1. Non-inferiority for primary endpoint (BCVA): H_{01} versus H_{A1}
2. Superiority for key secondary endpoint 1 (PDR): H_{03} versus H_{A3}
3. Superiority for primary endpoint (BCVA): H_{02} versus H_{A2}
4. Superiority for key secondary endpoint 2 (CI-DME): H_{04} versus H_{A4}

Or equivalently, the tests will be conducted using the following graphical approach (Bretz et al, 2009).



To be noted that the conclusion for each test will be based on its main analysis (e.g., primary analysis of primary estimand for BCVA).

Additional testing will be performed for important secondary efficacy endpoint after the rejection of null hypotheses in H_1, H_2, H_3 and H_4. Details are described in Section 2.7.2.1.

2.6.3 Handling of missing values/censoring/discontinuations

The key secondary estimands and other supplementary estimands of interest are noted in Table 2-4 below together with their key attributes, including the handling of intercurrent events associated with the use of alternative treatments for DR or treatment of DME in the study eye.

Table 2-4 Key secondary and supplementary estimands

Endpoint	Estimand	Estimand definition	Analysis set	Data included in analysis	Statistical methods (including missing data strategy)
DRSS	Key secondary estimand 1	Difference in proportions of subjects with no PDR at Week 54 excluding the effect of alternative DR treatment(s) / relevant DME treatment(s)	FAS	All data captured until the start of alternative DR treatment(s) / relevant DME treatment(s) will be included	CMH test and weighted proportion difference as specified in Section 2.6.2.1; LOCF imputation / replacement for missing /censored data
DRSS	Supplementary estimand A1	Difference in proportions of subjects with no PDR at Week 54 regardless of alternative DR treatment(s) / relevant DME treatment(s)	FAS	All data captured will be included	CMH test and weighted proportion difference as specified in Section 2.6.2.1; LOCF imputation for missing data
Center-involved DME	Key secondary estimand 2	Difference in proportions of subjects with CI-DME up to Week 54	FAS	All data captured will be included; subjects who receive alternative DR treatment(s) / relevant DME treatment(s) will be classified as with CI-DME	CMH test and weighted proportion difference as specified in Section 2.6.2.2

2.6.3.1 PDR status at Week 54

Handling of intercurrent events

Use of alternative DR treatment / relevant DME treatment (e.g., anti-VEGFs/PRP other than the assigned study treatment, corticosteroids and vitrectomy in Table 2-1) in the study eye is considered as the important intercurrent event for the key secondary estimand 1, taking into account that those treatments can potentially improve the DR condition, and thus may confound the treatment effect of interest.

For subjects who received those alternative treatments for DR in the study eye before Week 54, the data collected after this event will be censored and the value at Week 54 will be replaced by their last observation prior to this event.

Handling of missing values not related to intercurrent event

Missing DRSS values will be imputed by LOCF as a main approach. Observed values from both scheduled and unscheduled visits will be used for the LOCF imputation. Baseline value will not be carried forward for subjects with no post-baseline value.

2.6.3.2 Center-involved DME up to Week 54

Handling of intercurrent events

Use of alternative DR treatment / relevant DME treatments (e.g., anti-VEGFs other than the assigned study treatment, corticosteroids, focal/grid laser in Table 2-1) in the study eye is considered as the important intercurrent event for the key secondary estimand 2, taking into account that use of these treatments potentially indicates lack of efficacy of study treatment in preventing CI-DME.

Subjects who received those alternative treatments for DME in the study eye before Week 54 will be classified as having developed CI-DME.

Handling of missing values not related to intercurrent event

For subjects who discontinued the study before Week 54, if there is any record of CI-DME event (i.e., CSFT ≥280 μm) or DME treatment before discontinuation, the subject will be classified as having CI-DME. Otherwise, the subject will be classified as not having CI-DME.

Missing CSFT values will be imputed by LOCF as a general approach. Observed values from both scheduled and unscheduled visits will be used for the LOCF imputation. Baseline value will not be carried forward for subjects with no post-baseline value.

2.6.4 Supportive analyses

2.6.4.1 PDR status at Week 54

Sensitivity analyses

For the first key secondary estimand, to assess the robustness of the results in terms of the assumptions underlying the data handling approach mentioned above, sensitivity analyses using alternative methods of handling missing or confounded data other than LOCF will be performed.

A MICE method will be used in the sensitivity analysis. The imputation is on the DRSS 12-level scale. PDR status will then be derived from the imputed DRSS. Regression models including the same adjusting factors in the CMH test and DRSS values at each visit will be used for imputation. DRSS values collected after start of alternative treatment for DR (e.g., anti-VEGFs/PRP other than the assigned study treatment, corticosteroids and vitrectomy in Table 2-1) are not included in the imputation model.

Additional sensitivity analysis may be conducted for the first key secondary estimand using the LOCF approach by excluding subjects with “Ungradable” for DRSS at baseline.

The **supplementary analysis** for supplementary estimand A1 will include data after use of alternative DR treatment / relevant DME treatment.

In addition to the sensitivity analyses and supplementary analyses mentioned above, other supportive analyses are specified below:

Subgroup analyses will be conducted to assess the consistency of treatment effect across baseline HbA1c categories, CRC assessed baseline DR severity categories (see Section 2.2.1) and CRC assessed baseline CSFT categories (see Section 2.2.1) considering the FAS only. They will be conducted using the framework for the first key secondary estimand only:

- Subgroup analyses will be conducted using the weighted proportion difference described in Section 2.6.2.1 but fitted by category of each of the subgroups. Subgroup variables that are used as adjusting factors will be removed from the analysis model.
- In case of analyses on subgroups with extremely imbalanced sample sizes, the subgroup levels can either be combined, if appropriate, or the extremely small subgroup will be excluded while fitting the analysis model.
- Subgroup analysis results will be presented using forest plots.

Additional subgroup analyses will be performed to evaluate the impact of COVID-19 pandemic.

Summary statistics:
Descriptive statistics of PDR status at Week 54 will use observed data and FAS with and without censoring data after use of alternative DR treatment / relevant DME treatment in the study eye.

If the number of discontinuations crossed the quality tolerance limit (see Section 2.3.2), **additional analyses** will be conducted to evaluate the impact of discontinuation:

- Proportion of subjects with no PDR with error bars representing ± SE will be presented by visit and by treatment group using bar plots. Separate plots will be provided for subjects who discontinued versus not discontinued study treatment and for subjects who discontinued versus not discontinued study. This will be conducted using the same framework of the key secondary estimand 1 (FAS with censoring of data collected after use of alternative DR treatment/relevant DME treatment in the study eye, and missing/censored values imputed/replaced using LOCF).
- Evaluate the treatment effect using the hypothetical strategy with the following attributes:

  Population: subjects with PDR (i.e., the entire study population)

  Endpoint: proportion of subjects with no PDR at Week 54

  Treatment: brolucizumab 6 mg/PRP

  Intercurrent events: use of alternative DR treatment / relevant DME treatment, which will be handled by LOCF as described in Section 2.5.3; study treatment discontinuation (PDR status after treatment discontinuation will be treated as missing), which will be handled by prediction of hypothetical trajectories, assuming treatment discontinuation had not occurred and subjects who discontinued would behave similarly as those who

did not on the same treatment arm. If both intercurrent events occurred to the same subject, data will be handled according to the first event

Summary measure: difference in proportions of no PDR

To analyze the hypothetical estimand, a generalized linear mixed model (GLMM) assuming MAR will be used on PDR status (dichotomized from DRSS, including data handled by LOCF to address the use of alternative treatment). The GLMM will include treatment, visit, age category (<55, >=55), baseline DR Severity category (NPDR, Mild or moderate PDR, High-risk PDR or worse), region (US and Canada, East Asia, Other) and treatment by visit interaction as fixed-effect terms and will be implemented using a marginal model with an unstructured covariance matrix to model the correlations among repeated (binary) measures of PDR status. If the GLMM with an unstructured covariance matrix does not converge, a more restricted covariance matrix can be considered in the following order until convergence is reached: Toeplitz, first-order autoregressive, compound symmetry and variance components. Treatment difference in proportions (brolucizumab - PRP) at Week 54 will be estimated using the LSM and 95% CI.

Given reasonable assumption(s) (e.g., principal ignorability), additional analysis may be performed to evaluate the treatment effect on the principal stratum of subjects who would not discontinue treatment regardless of treatment assignment.

2.6.4.2 Center-involved DME up to Week 54

Subgroup analyses will be conducted to assess the consistency of treatment effect across baseline HbA1c categories, CRC assessed baseline DR severity categories (see Section 2.2.1) and CRC assessed baseline CSFT categories (see Section 2.2.1) following the similar approaches for first key secondary endpoint.

Additional subgroup analyses will be performed to evaluate the impact of COVID-19 pandemic.

To investigate the **development of CI-DME over time**, Kaplan-Meier (KM) estimates of the time to first CI-DME event over time up to Week 54 for each treatment group will be presented in a plot, where use of alternative DR treatment / relevant DME treatment mentioned in Table 2-1 to treat DME will be treated as a CI-DME event. In the time-to-event analysis, subjects without any CI-DME event will be censored at Week 54 analysis cut-off date or study discontinuation date, whichever occurs first.

Summary statistics:

- Descriptive statistics of having CI-DME at each visit will use observed data and the FAS, regardless of use of alternative DR treatment / relevant DME treatment as a CI-DME event.

In addition, fluid status (i.e., presence/absence of IRF and SRF) by visit will be listed for the study eye, with censored or missing data replaced by LOCF. If baseline visit reported as “CANNOT GRADE”, then it will be considered as “Absent”; if post-baseline visit is reported as “CANNOT GRADE”, then it will be considered as missing.

2.7 Analysis of secondary efficacy objectives

2.7.1 Secondary endpoints

All endpoints related to secondary objectives are defined with respect to the study eye.

2.7.1.1 Endpoints related to diabetic retinopathy status:

- Proportion of subjects with at least 2 steps improvement from Baseline in ETDRS DRSS at Week 54 and Week 96
- Proportion of subjects with at least 3 steps improvement from Baseline in ETDRS DRSS at Week 54 and Week 96
- Proportion of subjects with no PDR at Week 96

Table 2-5 and Table 2-6 describe the definition of a 2-step and a 3-step change, respectively, for each (non-missing) baseline and post-baseline DRSS based on the 12-level scale (Table 2-3). Improvement and worsening of at least 2 or 3 steps in DRSS are defined as below:

- ≥2-step improvement: DRSS (12-level scale) at the visit – DRSS (12-level scale) at Baseline ≤-2
- ≥3-step improvement: DRSS (12-level scale) at the visit – DRSS (12-level scale) at Baseline ≤-3
- ≥2-step worsening: DRSS (12-level scale) at the visit – DRSS (12-level scale) at Baseline ≥2
- ≥3-step worsening: DRSS (12-level scale) at the visit – DRSS (12-level scale) at Baseline ≥3

Table 2-5 Definition of 2-step change in DRSS on the 12-level scale

	Post-Baseline		
Baseline	**≥2-step improvement**	**No change or change <2 steps**	**≥2-step worsening**
1	-	1, 2	3 or higher
2	-	1, 2 or 3	4 or higher
3	1	2, 3, or 4	5 or higher
4	1 or 2	3, 4, or 5	6 or higher
5	3 or lower	4, 5, or 6	7 or higher
6	4 or lower	5, 6, or 7	8 or higher
7	5 or lower	6, 7, or 8	9 or higher
8	6 or lower	7, 8, or 9	10 or higher
9	7 or lower	8, 9, or 10	11 or 12
10	8 or lower	9, 10, or 11	12
11	9 or lower	10, 11, or 12	-
12	10 or lower	11, 12	-

Table 2-6 Definition of 3-step change in DRSS on the 12-level scale

Baseline	Post-Baseline		
	≥3-step improvement	No change or change <3 steps	≥3-step worsening
1	-	1, 2 or 3	4 or higher
2	-	1, 2, 3 or 4	5 or higher
3	-	1, 2, 3, 4 or 5	6 or higher
4	1	2, 3, 4, 5 or 6	7 or higher
5	1 or 2	3, 4, 5, 6 or 7	8 or higher
6	3 or lower	4, 5, 6, 7 or 8	9 or higher
7	4 or lower	5, 6, 7, 8 or 9	10 or higher
8	5 or lower	6, 7, 8, 9 or 10	11 or 12
9	6 or lower	7, 8, 9, 10 or 11	12
10	7 or lower	8 or higher	-
11	8 or lower	9 or higher	-
12	9 or lower	10 or higher	-

2.7.1.2 Endpoints related to visual acuity:

- Area under the curve (AUC) in change from Baseline in BCVA up to Week 54 and Week 96

Following the approach used in Gross et al (2015), the AUC in change from Baseline in BCVA up to Week 54 is referred to as the averaged change from Baseline in BCVA at each visit up to Week 54, which will be calculated as (BCVA at Week 6 + BCVA at Week 12 + ... + BCVA at Week 54) / number of visits with valid BCVA data from Week 6 to Week 54 – BCVA at Baseline.

Similarly, the AUC in change from Baseline in BCVA up to Week 96 is referred to as the averaged change from Baseline in BCVA at each visit up to Week 96, which will be calculated as (BCVA at Week 6 + BCVA at Week 12 + ... + BCVA at Week 96) / number of visits with valid BCVA data from Week 6 to Week 96 – BCVA at Baseline.

2.7.1.3 Endpoints related to ocular complications:

- Proportion of subjects developing vision-threatening complications associated with DR up to Week 54 and Week 96
- Proportion of subjects with CI-DME up to Week 96

The definition of CI-DME is the same as key secondary endpoint described in Section 2.6.1.2.

The vision-threatening complications associated with DR are defined as any event of the following list occurring in the study eye at any time point after Baseline:

- CI-DME as described in Section 2.6.1.2
- Retinal detachment
- Vitreous hemorrhage
- Neovascular glaucoma, iris/ anterior chamber angle neovascularization
- Vitrectomy for DR complications

2.7.2 Statistical hypothesis, model, and method of analysis

2.7.2.1 Additional confirmatory testing

Confirmatory hypothesis testing for the proportion of subjects with at least 2 steps improvement from baseline in DRSS at Week 54 (see Section 2.7.1.1) will be performed after the proof of efficacy is demonstrated sequentially for the four hypotheses specified for the primary and key secondary endpoints (see Section 2.6.2.3). Superiority of brolucizumab 6 mg versus PRP will be tested at a one-sided level of 0.025. The overall type I error rate of level 0.025 is still maintained within this multiple testing strategy.

2.7.2.2 General analysis specifications

Analysis of binary endpoints (DR status and ocular complications)

For each endpoint, the difference in proportions between treatment arms will be estimated using the weighted average of the proportion differences over adjusting factors using the Mantel-Haenszel weights. Adjusting factors will be the same as for the CMH test for first key secondary endpoint (baseline DR Severity category, age category and region). The corresponding 95% CI for the difference will be calculated based on normal approximation for binomial proportions.

The nominal p-value of treatment comparison for each endpoint will be obtained from the CMH test. The CMH test will include the same factors as for the CMH test for first key secondary endpoint as mentioned in Section 2.6.2.1.

Analysis of continuous endpoints (visual acuity)

For each endpoint, an ANCOVA model will be fitted with the same factors and covariate used in the analysis of primary endpoint as mentioned in Section 2.5.2. The LSM estimates, 95% CI for the corresponding treatment difference and nominal p-value for treatment comparison will be obtained from the ANCOVA model.

2.7.3 Handling of missing values/censoring/discontinuations

Diabetic retinopathy status

Similar to the first key secondary endpoint, DRSS values collected after use of alternative DR treatment / relevant DME treatment in the study eye will be censored and will be replaced by their last observation prior to this event.

Missing DRSS values will be imputed by LOCF, following the same approach as first key secondary endpoint.

Visual acuity

Similar to the primary endpoint, BCVA values collected after use of alternative DR treatment / treatment of DME in the study eye will be censored and will be replaced by their last observation prior to this event.

Missing BCVA values will be imputed by LOCF, following the same approach as primary endpoint.

Ocular complications

For CI-DME up to Week 96, subjects who received alternative treatment for DME will be classified as having developed CI-DME.

For subjects who discontinue early from the study, their status will be defined according to the records of corresponding event in the clinical database before discontinuation.

2.7.4 Supportive analyses

Diabetic retinopathy status

To evaluate the **DR status over time**, descriptive statistics of the DRSS ≥2 steps improvement, ≥2 steps worsening, ≥3 steps improvement, ≥3 steps worsening and PDR status by visit and treatment will use observed data and the FAS, with censoring data after use of alternative treatment for DR in the study eye. Bar chart for proportion of each treatment arm will be plotted by visit.

If the number of discontinuations crossed the quality tolerance limit (see Section 2.3.2), **additional analyses** will be conducted to evaluate the impact of discontinuation on the proportion of subjects with at least 2 steps improvement from baseline in ETDRS DRSS score at Week 54, following a similar approach as described in Section 2.6.4.1 for the first key secondary endpoint.

Visual acuity

To further understand the profile of BCVA at end of study, the following **categorical changes** will be summarized by treatment group, with the same handling approach for censored/missing values as primary analysis. BCVA values collected after start of alternative DR treatment / relevant DME treatments will be censored and imputed using LOCF.

- Number and percentage of subjects with a gain in BCVA of ≥5, ≥10 and ≥15 ETDRS letters from Baseline to each post-baseline visit
- Number and percentage of subjects with a loss in BCVA of ≥5, ≥10 and ≥15 ETDRS letters from Baseline to each post-baseline visit
- Number and percentage of subjects with an absolute BCVA ≥84 ETDRS letters at each scheduled visit

To assess the **BCVA change over time**, the BCVA change at each visit up to Week 54/Week 96 will be analyzed using the same approach as the analysis for the primary endpoint. Line plot on LSM (± SE) by visit will be provided for both treatment arm.

Descriptive statistics of BCVA values and changes from Baseline at each visit will use observed data and the FAS, with and without censoring data after use of alternative DR treatment / relevant DME treatment in the study eye.

Ocular complications

To investigate **development of CI-DME over time**, KM estimates of the time to first CI-DME event over time up to Week 96 for each treatment group will be presented in a plot, counting use of DME treatment as a CI-DME event. In the time-to-event analysis, subjects without any CI-DME event will be censored at study completion/discontinuation date.

Descriptive statistics of having CI-DME at each visit up to Week 96 will use observed data and the FAS, regardless of use of alternative DR treatment / relevant DME treatment.

For **each component** of the vision-threatening complications related to DR, descriptive statistics of having at least one event up to Week 54/Week 96 will use observed data and the FAS, regardless of receiving alternative DR treatment / relevant DME treatment. The number and percentage of subjects who received alternative DR treatment / relevant DME treatment mentioned in Table 2-1 will also be summarized.

2.8 Safety analyses

Safety endpoints are based on the variables from safety assessments, which include:

- Adverse events
- Intraocular pressure (IOP) for the study eye
- Loss in BCVA for the study eye
- Vital signs
- Laboratory results

There is no formal safety hypothesis in this study. All safety analyses will be performed using the safety analysis set.

2.8.1 Adverse events (AEs)

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

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

The number (and percentage) of subjects with TEAEs will be summarized at each analysis time point (Week 54, Week 96) in the following ways:

Table 2-7 TEAE summary

TEAE summary	AE categories		
	Ocular AE in the study eye	Ocular AE in the fellow eye	Non-ocular AE
AEs by primary SOC and PT	Y		Y
AEs by primary SOC and PT (including events with onset date after start of alternative DR treatment / relevant DME treatment)	Y	Y	Y
Frequent AEs by PT‡	Y		Y
AEs by maximum severity by SOC and PT	Y		Y
AEs related to study treatment by SOC and PT	Y		Y
AEs related to study procedure by SOC and PT	Y		Y
AEs leading to permanent discontinuation of study treatment by SOC and PT	Y		Y

TEAE summary	AE categories		
	Ocular AE in the study eye	Ocular AE in the fellow eye	Non-ocular AE
AEs leading to temporary interruption of study treatment by SOC and PT	Y		Y
SAEs by SOC and PT	Y		Y
SAEs by SOC and PT (including events with onset date after start of alternative DR treatment / relevant DME treatment)	Y	Y	Y
SAEs related to study treatment by SOC and PT	Y		Y
SAEs related to study procedure by SOC and PT	Y		Y
†: ≥2 % (or other cutting point as appropriate) in any treatment group for a given PT. Additional summaries may be also conducted to evaluate the impact of COVID-19 pandemic.			

In all summary tables listed above, unless otherwise specified, data collected after the subject started alternative DR treatment / relevant DME treatment in the study eye will be censored.

If an AE started on the same day as the start of alternative DR treatment / relevant DME treatment for a subject, the AE will be excluded from the summary table, unless this AE led to study drug withdrawal (in such a case, the AE would be included in the analysis).

Subject listings of all adverse events will be provided. Deaths, other SAEs (i.e., other serious or clinically significant non-fatal adverse events), AEs resulting in permanent treatment discontinuation and AEs of special interest will be listed separately.

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

If the number of discontinuations crossed the quality tolerance limit (see Section 2.3.2), summaries of ocular and non-ocular AEs/SAEs by SOC and PT will also be provided for subjects discontinued versus not discontinued treatment/study.

2.8.1.1 Adverse events of special interest / grouping of AEs

Incidence of adverse events of special interest (AESI) will be tabulated by treatment arm.

AESIs and other safety topics of interest will be identified via the RTH258 electronic case retrieval strategy (eCRS). The eCRS that is current at the time the database lock will be used and the AESIs and other safety topics of interest will be identified where the flag “Core safety topic risk (SP)” = ‘Y’.

2.8.1.2 Adverse event reporting for clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov, two required tables on TEAEs which are not serious adverse events with an incidence greater than 2% (or other cutting point as appropriate) and on TEAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the SAF.

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

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

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

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

2.8.2 Deaths

A summary table of treatment emergent deaths will be presented by primary SOC and PT. In addition, a separate summary of post-treatment deaths will be provided by primary SOC and PT.

All deaths recorded in the clinical database will be listed.

2.8.3 Laboratory data

Laboratory data will be presented graphically using boxplots of absolute change from baseline values by treatment arm and visit. A summary table with number and percentage of subjects satisfying the criteria representing clinically relevant abnormalities given in Section 5.3 at any visit will be presented. Data after use of alternative DR treatment / relevant DME treatment in the study eye are censored and are not included. A listing for subjects satisfying at least one criterion in Table 5-1 at any visit will also be presented.

2.8.4 Other safety data

2.8.4.1 IOP

Descriptive summaries of change from Baseline in pre-treatment IOP values for the study eye will be presented graphically at each scheduled study visit by treatment arm, considering line plots of the mean change in IOP values with error bars representing ± SE. The x-axis will be study visit and the y-axis will be the change from Baseline value. No summary by visit tables will be provided.

The number and percentage of subjects with pre-treatment IOP >30 mmHg at any visit will be summarized.

Summary tables with number and percentage of subjects with an IOP increase of ≥10, ≥20 mmHg from pre-treatment to post-treatment at any visit for the study eye will be presented.

A summary table with number and percentage of subjects with observed pre-treatment IOP ≥ 21mmHg at 3 consecutive scheduled visits will be presented.

A visit with missing pre-treatment IOP is considered to meet the ≥ 21 mmHg criterion if the preceding and the following visits meet the criterion that pre-treatment IOP ≥ 21 mmHg. For example, if schedule visit X has missing pre-treatment IOP and pre-treatment IOP ≥ 21 mmHg

is observed for both visit X-1 and X+1, the subject is considered to meet the criteria at visit X as well. Otherwise, the visit with missing pre-treatment IOP is considered as not meeting the ≥ 21 mmHg criterion.

Data after use of alternative DR treatment / relevant DME treatment in the study eye are censored and are not included.

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

2.8.4.2 Loss in BCVA

The number and percentage of subjects with a loss in BCVA ≥15, ≥30 letters (for the study eye) from Baseline to the last visit, and maximum loss at any visit will be presented. BCVA values after use of alternative DR treatment / relevant DME treatment in the study eye are censored and are not included.

BCVA data (for the study eye) for subjects presenting a loss in BCVA ≥15 letters from Baseline at any post-baseline visit will be listed.

2.8.4.3 Vital signs

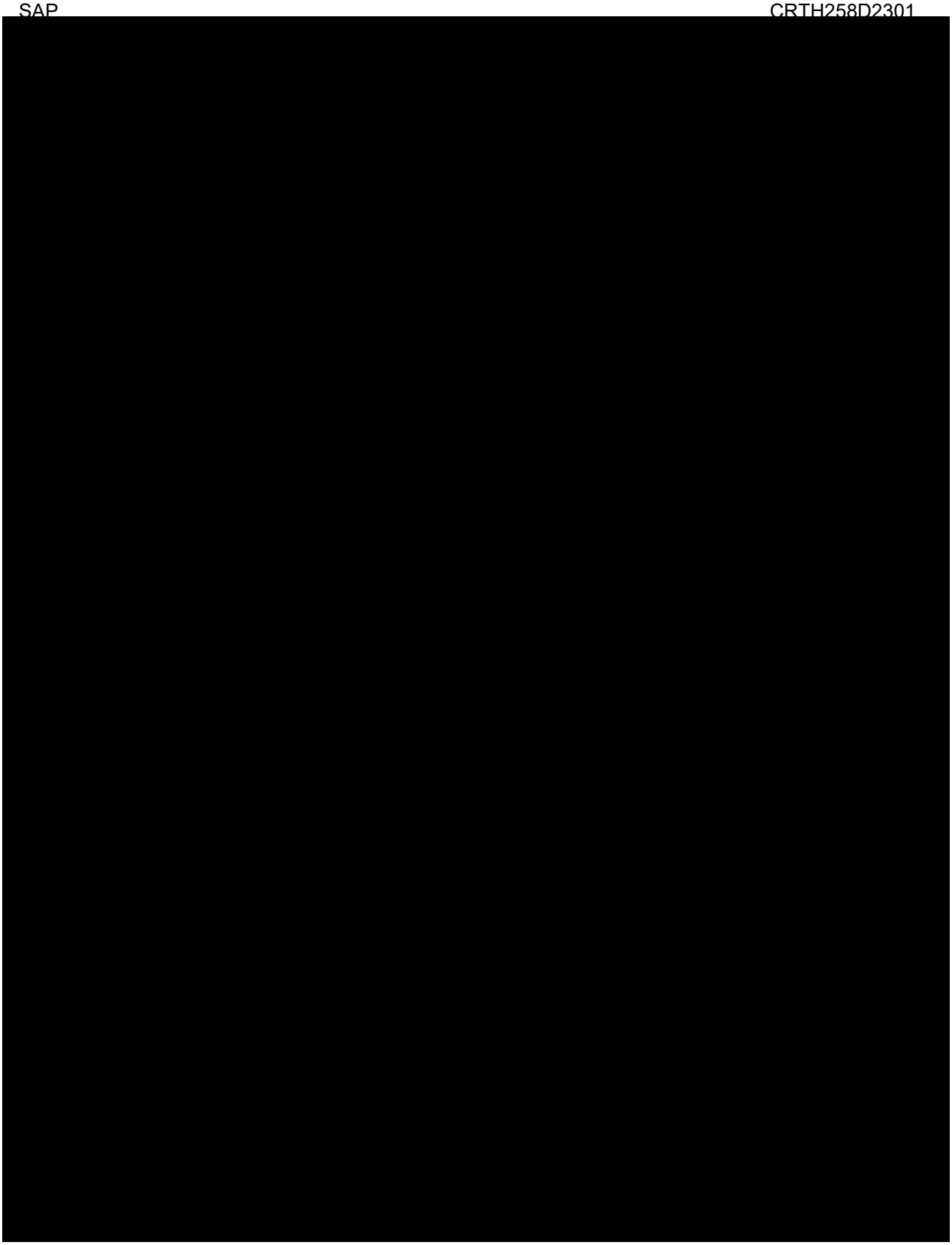
A summary table with number and percentage of subjects satisfying the criteria given in Table 5-2 of Section 5.3 at any visit will be presented. A listing for subjects satisfying at least one criterion in Table 5-2 will also be presented.

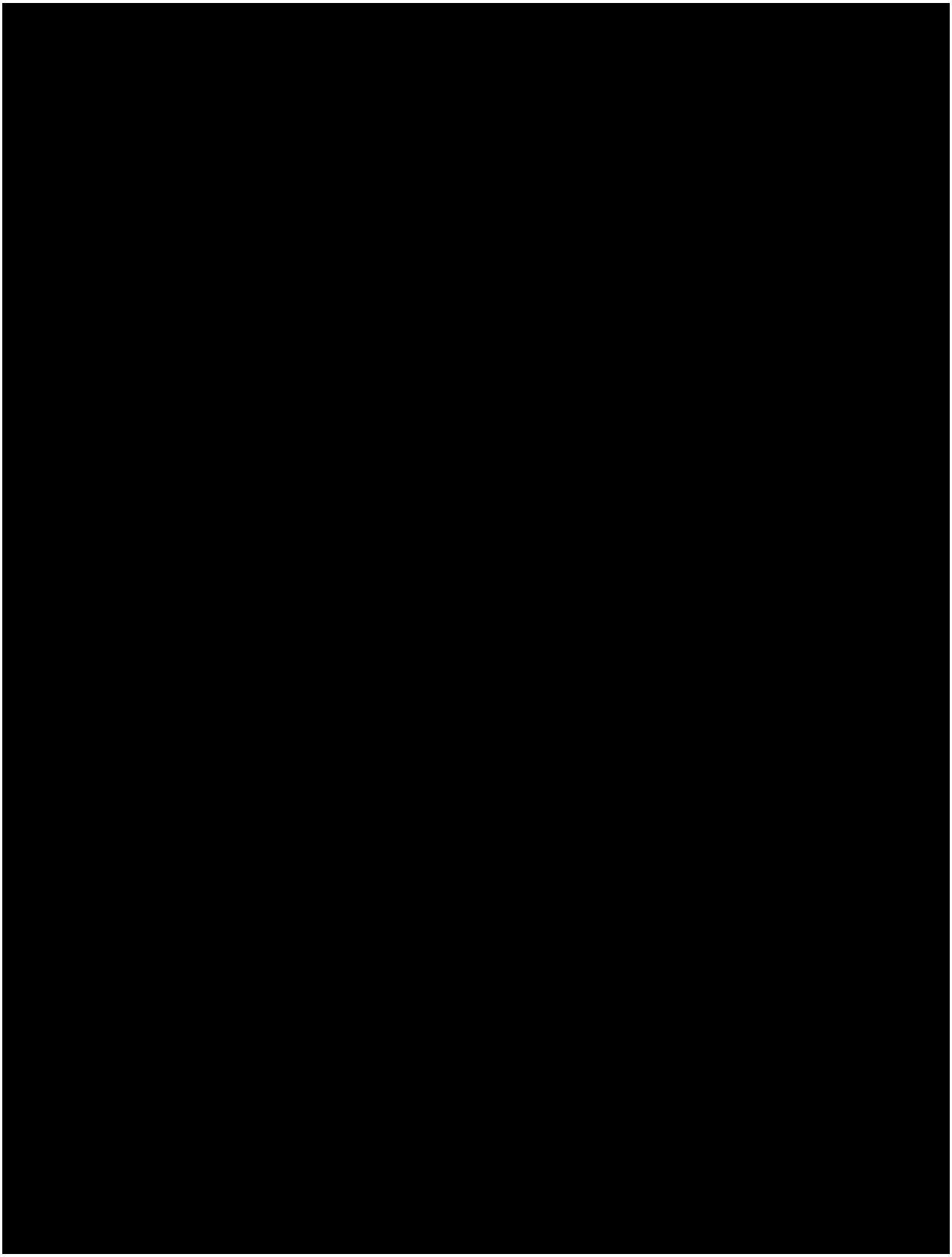
A line plot of mean change from Baseline in the vital sign parameter by study visit and treatment arm with error bars representing ± standard error will be presented. The x-axis will be study visit and the y-axis will be the mean change from baseline value.

Data after use of alternative DR treatment / relevant DME treatment in the study eye are censored and are not included.

2.9 Pharmacokinetic endpoints

Not applicable.



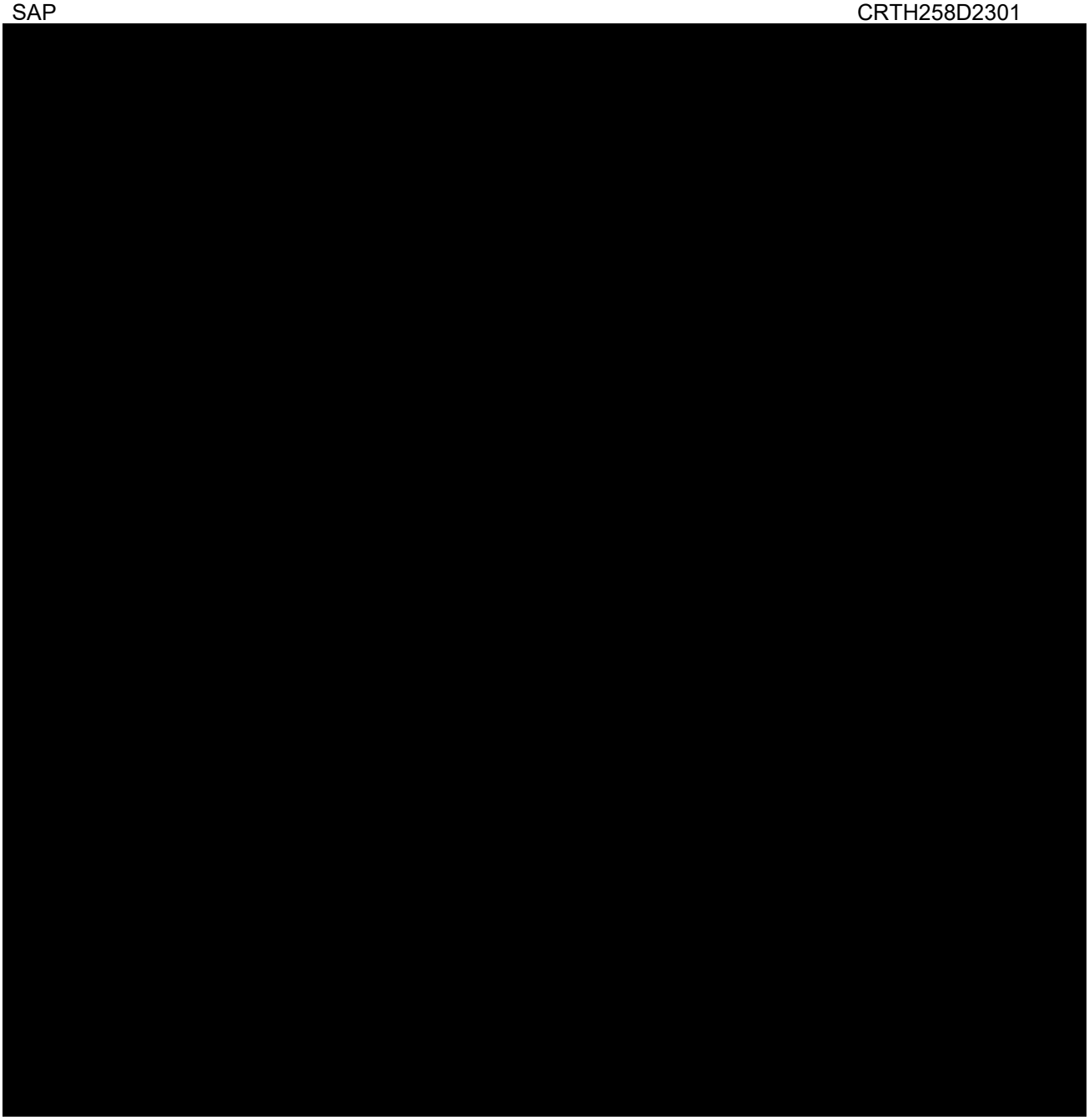


[redacted]

2.11 Biomarkers

Not applicable.

[redacted]



2.13 Interim analysis

The database including all Week 54 data will be freezed once all initially planned number of subjects have completed the Week 54 visit or discontinued study prior to Week 54. The primary analysis based on Week 54 data will be derived from this database. For event-driven analyses (e.g., time-to-event endpoints and AEs), Week 54 cut-off date will be derived at subject level, and only events occurred prior to or on the cut-off date will be included in the primary analyses. Formal testing of the primary endpoint and key secondary endpoints will be performed at the primary analysis time point.

3 Sample size calculation

A sample size of 300 subjects per arm will allow the assessment of brolucizumab 6 mg versus PRP for non-inferiority with respect to the primary endpoint and superiority with respect to the key secondary endpoints.

To account for a drop-out rate of 15%, a total of approximately 706 (353 per arm) subjects will be randomized.

3.1.1 Primary endpoint(s)

A sample size of 300 subjects per arm will allow assessment of non-inferiority (using a non-inferiority margin of 4 ETDRS letters) of brolucizumab 6 mg versus PRP with respect to the change from Baseline in BCVA at Week 54. Assuming that the BCVA changes follow a normal distribution with equal means between treatments, and a common standard deviation of 10 letters, for a one-sided alpha level of 0.025, there is >99% power to reject the null hypothesis that brolucizumab 6 mg is inferior to PRP. Sensitivity to the assumptions used to assess power for both non-inferiority and superiority testing is shown in Table 3-1.

Table 3-1 Power for primary endpoint

True treatment difference for brolucizumab vs PRP (letters)	SD (letters)	Power for non-inferiority test	Power for superiority test
0	10	> 99%	2.5%
0	13	96%	2.5%
3	10	> 99%	96%
3	13	> 99%	81%
5	10	> 99%	> 99%
5	13	> 99%	> 99%

3.1.2 Secondary endpoint(s)

A sample size of 300 subjects per arm will allow assessment of superiority of brolucizumab 6 mg versus PRP with respect to increasing the proportion of subjects with no PDR at Week 54. Assuming that the proportion of such events in the PRP arm is 15%, and the difference in proportion is 11% (i.e., the proportion in the brolucizumab arm is 26%), for a one-sided alpha level of 0.025, nominally there is 90% power to reject the null hypothesis that brolucizumab 6 mg is not superior to PRP.

A sample size of 300 subjects per arm will allow assessment of superiority of brolucizumab 6 mg versus PRP with respect to reducing the proportion of subjects with CI-DME up to Week 54. Assuming that the proportion of such events in the PRP arm is 16%, and the difference in proportion is 9% (i.e., the proportion in the brolucizumab arm is 7%), for a one-sided alpha level of 0.025, nominally there is 92% power to reject the null hypothesis that brolucizumab 6 mg is not superior to PRP.

The above calculations use the normal approximation for the binomial distribution with a continuity correction.

4 Change to protocol specified analyses

In Table 2-1 from the protocol, to compare the effect of brolucizumab relative to PRP on diabetic retinopathy status (secondary objective), the wording "Change from Baseline" is changed to "Step-change from Baseline" in Table 1-1 from Section 1.2 of this document, to clarify that "change" refers to 2- or 3- step change as described in Section 2.7.1.1.

Additional subgroup analysis will be performed by prior anti-VEGF treatment in the study eye for primary endpoint, unless the sample size is extremely small in this subgroup (see Section 2.2.1).

Since presence of CI-DME in the study eye at Screening or Baseline was assessed by investigator, a substantial number of subjects has baseline CSFT ≥280 µm (assessed by CRC). Therefore, additional subgroup analyses will be performed by baseline CSFT categories in the study eye for primary and key secondary endpoints (see Section 2.2.1) to investigate whether the treatment effect is consistent across baseline CSFT categories.

Confirmative hypothesis testing in relation to additional secondary endpoint is introduced in Section 2.7.2.1.

Across this document, the wording "alternative DR treatment / relevant DME treatment" is used to unify the description of corresponding analyses that are related to alternative treatment.

No other changes from protocol specified analysis was made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

No imputation will be made to the start date and end date of study treatment.

5.1.2 AE date imputation

5.1.2.1 AE start date imputation

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

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

The following matrix explains the logic behind the imputation.

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

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
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 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.

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

5.1.3 Concomitant medication (CM) date imputation

5.1.3.1 Concomitant medication start date

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

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

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

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

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

The following matrix explains the logic behind the imputation.

	MON MISSING	**MON < TRTM**	**MON = TRTM**	**MON > TRTM**
YYYY MISSING	(1) 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.

5.1.3.2 Concomitant medication end date imputation

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

2. Else, if the CM end date month is missing, the imputed end date should be set to the earliest of the (treatment end date, 31DECYYYY, date of death).

3. If the CM end date day is missing, the imputed end date should be set to the earliest of the (treatment end date, last day of the month, date of death).

4. If the imputed CM end date is less than the existing CM start date, use the CM start date as the imputed CM end date.

5.1.4 Medical history date of diagnosis imputation

Completely missing dates and partially missing end dates will not be imputed. Partial dates of diagnosis will be compared to the treatment start date.

1. If DIAG year < treatment start date year
    a. and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY)
    b. else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY)
2. If DIAG year = treatment start date year
    a. and (DIAG month is missing OR DIAG month is equal to treatment start month), the imputed DIAG date is set to one day before treatment start date
    b. else if DIAG month < treatment start month, the imputed DIAG date is set to the midmonth point (15MON YYYY)
    c. else if DIAG month > treatment start month => data error

3. If DIAG year > treatment start date year => data error

5.2 AEs coding/grading

AEs are coded using the MedDRA terminology.

5.3 Laboratory parameters and vital signs derivations

Table 5-1 Clinically notable laboratory values

Test	Conventional Units	Critical Low	Critical High	Standard Units	Critical Low	Critical High	Non-numeric
Calcium	mg/dL	< 6.0	> 13.0	mmol/L	< 1.50	> 3.25	
Creatinine		NA	>3xULN				
Glucose	mg/dL	< 40	> 450	mmol/L	< 2.2	> 25.0	
Potassium	mEq/L	< 2.8	> 6.2	mmol/L	< 2.8	> 6.2	
Sodium	mEq/L	< 120	> 160	mmol/L	< 120	> 160	
HCG							Negative, inconclusive
Hematocrit	%	< 20	> 60	V/V	< 0.20	> 0.60	
Hemoglobin	g/dL	< 6.0	> 20.0	g/L	< 60	> 200	
Platelet	X10E3/uL	< 50	> 999	X10E9/L	< 50	> 999	
WBC	X10E3/uL	< 2.0	> 35.0	X10E9/L	< 2.0	> 35.0	

Table 5-2 Clinically notable vital signs

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

5.4 Statistical models

Primary analysis

ANCOVA

The following ANCOVA model will be used for the primary efficacy endpoint:

<change from Baseline in BCVA at Week 54> = intercept + treatment + Baseline BCVA + age category + Baseline DR category + Region + error.

For the above analysis, the data structure is one record per subject. The SAS PROC MIXED can be used to perform the ANCOVA analyses.

MICE

MICE method will be used in the sensitivity analysis for primary and first key secondary endpoints. This multiple imputation procedure contains three steps: imputation step, analysis step and pooling step.

In the imputation step, missing values for each visit are imputed. The SAS PROC MI with FCS statement can be used to perform the imputation. Multiple imputed datasets will be produced. To be noted that the imputed values will be restricted to the plausible range of values (e.g. 0-100 for BCVA), and the imputed values will be rounded to the nearest integer after all imputations are completed.

In the analysis step, the analysis values (e.g., change from Baseline in BCVA) are calculated for all imputed and observed values. The analysis model (e.g., ANCOVA for BCVA) will be run for each of the imputed datasets.

In the pooling step, the analysis results derived from the individual imputed datasets are combined using SAS PROC MIANALYZE. The estimate type statistics computed for each imputed dataset are listed in the MODELEFFECTS statement and the associated standard errors for each estimate are listed in the STDERR statement. The overall combined estimate, standard error, and confidence interval for each estimate statistic are reported by PROC MIANALYZE.

MMRM

The following MMRM will be used for the supportive analysis of the primary efficacy endpoint:

*<change from Baseline in BCVA at Week 54> = intercept + treatment + Baseline BCVA + age category + Baseline DR category + Region + visit + treatment*visit + error.*

For this analysis, the data structure is one record per subject per scheduled visit. The data will include all subjects and have records for all scheduled visits, regardless of whether the assessment was missed or not at a given visit. Missing values will NOT be imputed using LOCF and will be passed to the model as missing. The SAS PROC MIXED will be used to perform the analysis.

Key secondary analysis

MH weighted proportion difference and CMH test

The key secondary endpoints will be analyzed using MH weighted proportion difference and CMH test.

The difference in proportion between treatment groups will be estimated using the weighted average of the proportion differences over adjusting factors using the MH weights, as follows:

$$w_i = \frac{\frac{n_{i0}n_{i1}}{n_{i0}+n_{i1}}}{\sum_{k=1}^{K}\frac{n_{k0}n_{k1}}{n_{k0}+n_{k1}}}$$

where i (i = 1,2, … , K) indicates a specific analysis stratum (a specific category within the adjusting factor, or a specific combined category when there are multiple adjusting factors), and n_{ij}= number of subjects within analysis stratum i and treatment group j (j = 0, 1).

The SAS PROC FREQ can be used to calculate the MH weighted proportion difference, with COMMONRISKDIFF option in the TABLE statement.

The SAS PROC FREQ with CMH option in the TABLE statement can be used to perform CMH test. The SAS procedure produces a two-sided p-value by default. The one-sided p-value can be manually converted in the following way:

- If the direction of the weighted proportion difference supports a better efficacy of brolucizumab, the two-sided p-value will be converted to a one-sided p-value by dividing by two.
- If the direction of the weighted proportion difference does not support a better efficacy of brolucizumab, the one-sided p-value will be calculated as 1 – (the two-sided p-value divided by two).

KM analysis

Kaplan-Meier estimates of the proportion of the proportion of subjects with center-involved DME in the study eye up to Week 54 will be presented for each treatment arm. A corresponding 95% CI will be derived from the LOGLOG transformation, using SAS PROC LIFETEST, with CONFTYPE = LOGLOG.

GLMM

The following (marginal) GLMM will be used for the supportive analysis of proportion of subjects with no PDR at Week 54:

*Logit(<Proportion of subjects with no PDR>) = intercept + treatment + age category + Baseline DR category + Region + visit + treatment*visit.*

For this analysis, the data structure is one record per subject per scheduled visit. The data will include all subjects and have records for all scheduled visits, regardless of whether the assessment was missed or not at a given visit. Missing values will NOT be imputed using LOCF and will be passed to the model as missing. The SAS PROC GLIMMIX will be used to perform the analysis. The dependence between longitudinal outcomes will be modeled by specifying an R-side covariance structure using RAN DOM _RESIDUAL_ statement.

5.5 Rule of exclusion criteria of analysis sets

Important protocol deviations are defined in the Edit Check Specifications Document. Table 5-3 includes the important protocol deviations which lead to exclusion of a subject from one or more analysis sets for the Week 54 analysis.

Table 5-3 Important protocol deviations leading to exclusion from analyses

Deviation ID	Description of Deviation	Exclusion in Analyses
M_INCL01_ICF not obtained before start	Written informed consent not obtained	Exclude from all analyses
M_INCL02_Age less than 18 yrs	Patient less than 18 years of age at Screen	Exclude from PP analysis
M_INCL03_insufficient fundus retina image	No cooperation for sufficient fundus and retinal images	Exclude from PP analysis
M_INCL04_No diagnosis of Diabetes	Not diagnosed with type 1 or 2 DM, OR HbA1 >12% at Screening	Exclude from PP analysis

Deviation ID	Description of Deviation	Exclusion in Analyses
M_INCL05_Unstable meds for Diabetes	Medication administered for the management of DM is not stable as medically acceptable within 3 months prior to randomization	Exclude from PP analysis
M_INCL06_No PDR or evidence of PRP	No evidence of PDR in study eye or evidence of previous PRP	Exclude from PP analysis
M_INCL07_BCVA less than 34 study eye	BCVA less than 34 ETDRS letters at Screening and Baseline	Exclude from PP analysis
M_EXCL01_Confoundin g condition study eye with impact	Study Eye: Confounding ocular concomitant conditions or ocular disorders with impact	Exclude from PP analysis
M_EXCL03_ Med/procedure study eye with impact	Study Eye: Confounding concomitant medications or procedures with impact	Exclude from PP analysis
M_EXCL04_Systemic condition/trt w/impact	Systemic: Confounding systemic conditions or systemic treatments with impact	Exclude from PP analysis if a subject has received systemic anti-VEGF therapy at any time; Otherwise include in all analyses
M_TRT01_Missed treatment	Missed active treatment (not due to any safety event)	Exclude from PP analysis in RTH arm if any missed treatment during loading phase (not due to safety), or if at least 2 missed doses after loading (not due to safety); Otherwise include in all analyses
M_TRT02_Trt interval wrongly adjusted	A patient with no DA whose dosing interval wrongly reduced per protocol, or with DA, but wrongly extended per protocol	Exclude from PP analysis if subject receives 2 treatments on assessment visit prior to W54 when DAA=No
M_OTH03_Any other PD	Any other protocol deviation with impact on the efficacy assessments or safety of the patient	Exclude from PP analysis
M_WITH01_Treatment but consent withdrawn	Subject withdrew consent but continue to receive study medication.	Exclude from PP analysis

Table 5-4 lists the non-protocol deviations (analysis restrictions) that may lead to exclusion from per-protocol analysis. Analysis restrictions (ARs) address limitations in the evaluability which result from missing or confounded data with underlying background not qualifying as a PD (e.g., early study terminations, early treatment discontinuations, missing BCVA assessments).

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

Table 5-4 Non-protocol deviations (analysis restrictions)

AR ID	Description of AR	Category of reason	Exclusion in Analyses
AR_EST_01	Early study termination due to lack of efficacy	1	Include in all analyses
AR_EST_02	Early study termination due to safety concern	2	Include in all analyses

AR ID	Description of AR	Category of reason	Exclusion in Analyses
AR_EST_03	Early study termination due to reasons other than lack of efficacy/safety	0	Exclude from PP analysis if before Week 18; otherwise include in all analyses
AR_ETD_01	Early study treatment termination due to lack of efficacy	1	Include in all analyses
AR_ETD_02	Early study treatment termination due to safety concern	2	Include in all analyses
AR_ETD_03	Early study treatment termination due to reasons other than lack of efficacy/safety	0	Exclude from PP analysis if before Week 18; otherwise include in all analyses
AR_MD_01	No valid BCVA assessment after Baseline	0	Exclude from PP analysis

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

- Lack of efficacy of the study treatment (=1)
- Safety concern / tolerability of the study treatment (=2)
- Other (=0)

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

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

Table 5-5 summarizes the concepts of censoring for the key parameters BCVA and DRSS, as well as the details for the timing of censoring.

In case a subject has multiple PDs/ARs with impact on subject's evaluability the following rules are applied:

- A subject is excluded from an analysis set if at least one PD or AR with this consequence was identified (see Table 5-4).
- In case of multiple censoring time points censoring will be performed at the earliest.

Table 5-5 Censoring concepts for BCVA and DRSS

Analysis Set	Censoring concept for BCVA	Censoring concept for DRSS
FAS	Censoring of BCVA data after switch to alternative DR treatment / relevant DME treatment in the study eye: replacement using the last observation collected prior to the start of alternative DR treatment / relevant DME treatment (see Section 2.5.3) No other censoring related to PDs or ARs.	Censoring of DRSS data after switching to alternative DR treatment in the study eye: replacement using the last observation collected prior to the start of alternative DR treatment (see Section 2.6.3)

PPS	Censoring of BCVA data after switch to alternative DR treatment / relevant DME treatment in the study eye: replacement using the last observation collected prior to the start of alternative treatment DR/ relevant DME treatment (see Section 2.5.3) M_WITH02_Prohibit con and not withdrawn: censor at the last observation collected prior to the protocol deviation, replacement using the last observation collected prior to the protocol deviation M_COMD01_Prohibited medication or procedure: censor at the last observation collected prior to the protocol deviation, replacement using the last observation collected prior to the protocol deviation M_OTH01_Masking process not followed related to BCVA: censor the observation from the corresponding visit, replacement using the last observation collected prior to the protocol deviation M_OTH02_Assessment deviation related to BCVA: censor the observation for the corresponding visit, replacement using the last observation collected prior to the protocol deviation	No planned analysis on PPS

5.6 Subgroup analysis to evaluate the impact of COVID-19 pandemic

Since all subjects in this study were enrolled after the start of COVID-19, all subjects are exposed and analyses will be performed only for impacted versus non-impacted subjects.

Impacted subjects to COVID-19 up to Week X (X can be 54 or 96) are defined as subjects who:

- Missed at least one study treatment due to COVID-19 up to Week X, or
- Discontinued study/study treatment due to COVID-19 up to Week X, or
- Had reported COVID-19 infections (including suspected as per PTs in the Programming Dataset Specifications) up to Week X.

Non-impacted subjects to COVID-19 up to Week X are defined as subjects who:

- Did not miss any study treatment due to COVID-19 up to Week X, and
- Did not discontinue study/study treatment due to COVID-19 up to Week X, and
- Did not have reported COVID-19 infection (including suspected as per PTs in the Programming Dataset Specifications) up to Week X.

Demographics and baseline characteristics will be summarized separately for impacted and non-impacted subjects. Subgroup analyses will be conducted for the endpoints described in the testing strategy using the same model and analysis methods. In addition, ocular (for the study eye) and non-ocular AEs and SAEs will be summarized by primary SOC and PT.

6 Reference

Bretz F, Maurer W, Brannath W, Posch M (2009) A graphical approach to sequentially rejective multiple test procedures. *Statistics in Medicine*; 28(4): 586-604.

Gross JG, Glassman AR, Jampol LM, et al (2015) Panretinal Photocoagulation vs Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy: A Randomized Clinical Trial. *JAMA* p. 2137-2146.