NOVARTIS

Clinical Development

RTH258/Brolucizumab

CRTH258A2301E1 / NCT03386474

A 24-week, double-masked, multicenter, two-arm extension study to collect safety and efficacy data on brolucizumab 6 mg drug product intended for commercialization in patients with neovascular age-related macular degeneration who have completed the CRTH258A2301 study

Statistical Analysis Plan (SAP)

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27Sep2018	Before CDBL	Consistency with final analysis of core study	Reflect all changes discussed during dry run	See below

A summary of revisions to this SAP includes:

- Changes in wording to simplify and distinguish between extension Baseline/Week and core Baseline/Week (coBL/coWeek vs exBL/exWeek),
- Other baseline characteristics: changes in some categories and addition of some variables reflecting the treatment interval related to the transition period,
- BCVA and CSFT:
    - Changes in categories and baseline values considered for the shift tables
    - Removal of sensitivity analysis based on observed data without imputation and without censoring of assessments after start of alternative anti-VEGF treatment in the study eye, due to the low number of cases observed during the study conduct,
- Use of "q12 treatment status at Week 24" instead of Week 20 for consistency with the core study (q12 treatment status at Week 48/96),
- Adverse Events:
    - For summary tables, addition of the number and percentage of patients presenting AEs both during the extension study and during the last 6 months of the core study
    - Removal of table listing categories of AEs of potential relevance to t intravitreal anti-VEGF class but reference to the RTH258 nAMD electronic case retrieval strategy (eCRS) at the time of the core study CRTH258-C001 clinical database lock
- ADA: change in analysis to reflect what has been done in the core study
- ARs/PDs: as stated in the initial SAP, the list of ARs and PDs with their impact on the statistical analysis was added

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List of abbreviations

ADA	Anti-drug antibodies
AE	Adverse event
AR	Analysis Restriction
ATC	Anatomical Therapeutic Classification
BCVA	Best Corrected Visual Acuity
BLA	Biologic Licence Application
coBL	Core Study Baseline
coWeek	Core Study Week
CM	Concomitant Medication
CSFT	Central Subfield Thickness
CSR	Clinical Study report
DAA	Disease Activity Assessment
DBL	Database Lock
eCRF	Electronic Case Report Form
eCRS	Electronic Case Retrieval Strategy
EoS	End of Study
exBL	Extension Study Baseline
exWeek	Extension Study Week
IA	Interim Analysis
IOP	Intraocular Pressure
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Drug Regulatory Affairs
nAMD	Neovascular Age-related Macular Degeneration
PD	Protocol deviation
PT	Preferred Term
q8	Treatment every 8 weeks
q12	Treatment every 12 weeks
SAP	Statistical Analysis Plan
SE	Standard Error
SOC	System Organ Class
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) describes the analyses to be conducted after Database Lock (DBL).

This SAP describes the analysis according to Section 9 of the study protocol along with any additional analyses, specifications or deviations from the protocol.

1.1 Study design

This is a double-masked, multicenter, two-arm extension study. Patients recruited at US sites who completed the 96-week core study CRTH258A2301 (also referred to as RTH258-C001), regardless of the treatment group (brolucizumab 3 mg, brolucizumab 6 mg or aflibercept 2 mg) are eligible for inclusion in the extension study provided Visit 26/Week 96 in the core study is ≤ 12 weeks from the Baseline visit in the extension study. The time period between the End of Study visit (EoS) of the core study and the first visit of the extension study is referred to as the transition period. Patients who were treated with aflibercept during the core study will continue to receive aflibercept in the extension study. Patients who were treated with brolucizumab 3 mg or 6 mg in the core study will receive brolucizumab 6 mg in the extension study.

Enrolled patients receive three intravitreal injections of either brolucizumab 6 mg or aflibercept 2 mg according to the protocol specified dosing schedule. This extension study consists of 7 study visits at 4-week intervals, labeled Visit 1/Baseline to Visit 7/EoS over a period of 24 weeks.

The study eye will be the same eye that received brolucizumab or aflibercept study treatment in the core study.

Approximately 75 to100 patients who completed study CRTH258A2301 are expected to be enrolled in this study. This sample size is not based on a power calculation but depends on the number of patients in the core study fulfilling the eligibility criteria of the extension study.

The final analysis will be conducted on all enrolled patient data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

1.2 Study objectives and endpoints

The study objectives and endpoints are described in Table 1-1.

Table 1-1 Study objectives and related endpoints

Objective(s)	Endpoint(s)
To collect data on safety and efficacy of the brolucizumab 6 mg drug product intended for commercialization in patients with nAMD previously treated in CRTH258A2301 study to support comparability to the brolucizumab 6 mg drug product used in Phase III clinical studies	• Incidence and characteristics of treatment emergent adverse events (AE) • Loss in Best Corrected Visual Acuity (BCVA) of 15 letters or more from Baseline at each post-baseline visit • Change in BCVA from Baseline at each post-baseline visit • q12 treatment status at Week 24 • Change in Central Subfield Thickness (CSFT) from Baseline at each post-baseline visit • Anti-drug antibody (ADA) status at Baseline, Week 8, Week 16 and Week 24.

2 Statistical methods

2.1 Data analysis general information

The final analysis will be performed by Novartis using SAS Version 9.4. This SAP describes the analyses to be conducted after the final DBL.

No formal hypothesis testing is planned for this study. Neither the patient selection process nor the expected sample size support a valid comparison between aflibercept and brolucizumab. Therefore, descriptive analyses will be presented for the brolucizumab treatment group with selected analyses presented stratified by core study treatment group (brolucizumab 6 mg, brolucizumab 3 mg). Data for the aflibercept treatment group will be presented in listings, no analyses will be performed for this treatment group. [redacted]

Continuous variables will be summarized using the number of observations, mean, standard deviation, standard errors, median, quartiles, minimum and maximum values. Categorical variables will be summarized with number of observations, the number of observations for each category and the corresponding percent.

2.1.1 General definitions

2.1.1.1 Baseline and post-baseline definitions

Extension baseline (Day 1) is defined as the date of the first study treatment in the extension study. The extension baseline value for efficacy and safety variables is the last available value collected prior to the first study treatment.

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

The study day for an extension post-baseline scheduled or unscheduled visit is defined as:

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

The study day for a scheduled or unscheduled visit before extension baseline is defined as:

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

2.1.1.2 End of study/end of treatment day mapping

The end of study date is the date when a patient completes or discontinues the study. The "Date of Last Exposure" is the date of the last study treatment.

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

2.1.1.3 Unscheduled visits

Data collected at unscheduled visits (with the exception of data collected at unscheduled visits see Section 2.1.1.2) 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, summary of maximum decrease or increase from extension baseline for vital signs data and maximum letter loss in BCVA from extension baseline (exBL) at any visit.

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

2.1.1.4 Missing and implausible dates

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

2.2 Analysis sets

The Extension Safety Set will include all patients who enter this extension study and receive at least one injection of study treatment in this extension study.

The Extension Safety Set will be used for the descriptive analyses and listings related to both efficacy and safety for the brolucizumab treatment group and for the listings for the aflibercept treatment group.

Patients will be reported under the treatment they were randomized to in the core study (brolucizumab, aflibercept). Note: In the core study, patients in the safety set are analyzed according to the treatment group from which they received the majority of treatments up to and

including Week 44. All patients received the majority of their treatments according to the randomization during this time period in the core study.

2.3 Patient disposition, demographics and other baseline characteristics

Descriptive analyses and listings will be presented for the brolucizumab treatment group. Data for the aflibercept treatment group will be presented in listings.

2.3.1 Patient disposition

The following summaries will be included in the disposition table: Number and percent of patients who are enrolled into the study, treated, complete the study, discontinue the study (including reasons for discontinuation) and discontinue from study treatment (including reasons for discontinuation). In addition, disposition will be presented by core study treatment group (brolucizumab 3 mg, brolucizumab 6 mg).

The number and percent of patients who discontinue the study and who discontinue treatment will be presented by study visit.

The number and percent of patients treated by site will be presented.

A listing of patients who discontinue from the study and/or treatment early will be provided for both treatment groups. The listing will identify the visits completed and when the study or treatment was discontinued including the corresponding reasons.

Number and percent of patients with protocol deviations (PD) and analysis restrictions (AR) will be presented by deviation/restriction category for the broluzicumab treatment arm including corresponding listings.

2.3.2 Demographics

Age at extension baseline (both as a continuous variable and using categories (< 50, 50-64, 65-74, 75-84, ≥ 85 years)), gender, race, and ethnicity will be summarized.

Demographic data will be listed for both treatment groups.

2.3.3 Baseline Characteristics

The summary of baseline ocular characteristics will be presented separately for the study eye and the fellow eye and will include: primary diagnosis of nAMD, time since diagnosis of nAMD when entering the core study (months), whether nAMD is unilateral or bilateral when entering the core study, core and extension baseline BCVA (both as a continuous variable and using categories (≤ 55, 56-70, ≥ 71 letters)) and core and extension baseline CSFT (both as a continuous variable and using categories (< 400, ≥ 400µm)).

A summary of length of the transition period will be presented both as a continuous variable (weeks) and using categories (0 days, 1 day - ≤ 4 weeks, > 4 weeks - ≤ 8 weeks, > 8 weeks - ≤ 12 weeks, > 12 weeks).

In addition, a summary of length of time between last active treatment in the study eye in the core study and extension baseline (= first active treatment in the study eye in the extension

study), referred as the treatment interval related to the transition period, will be presented both as a continuous variable (weeks) and using categories (≤ 4 weeks, > 4 weeks - ≤ 8 weeks, > 8 weeks - ≤ 12 weeks, > 12 weeks - ≤ 16 weeks, > 16 weeks).

Furthermore, the distribution of core treatment group (brolucizumab 3 mg, brolucizumab 6 mg) and final treatment status (q12, q8) in the core study (coWeek 96) will be displayed.

The treatment interval based on final q12 (considering 84 days) /q8 (considering 56 days) status in core study versus the treatment interval related to the transition period will be summarized using categories (≤ 28 days, > 28 days).

Data will be listed for both treatment groups. In addition, a listing will display the treatment group under which the patient was analyzed for safety in the core study, the last active treatment received during the core study and, for the brolucizumab patients, final treatment status in the core study.

2.3.4 Medical history

The following describes the data to be recorded on the extension study eCRFs.

For patients where Core end of study visit date and Extension study first visit date occur on the same day the following data is recorded on the Medical History eCRF.

a) Medical histories which start before the core study and are ongoing at first visit of the Extension study

For patients where Core end of study visit date and Extension study first visit date do not occur on the same day the following data is recorded on the Medical History eCRF:

a) AEs which started during the core study and ended during the transition period
b) Medical conditions/events which start during the transition period and are ongoing at first visit of the Extension study
c) Medical conditions/events which start during the transition period and end during the transition period
d) Medical histories which start before the core study and end during the transition period
e) Medical histories which start before the core study and are ongoing at first visit of the Extension study
f) Procedures occurring during the transition period

Medical history (ocular and non-ocular) will be described together with current medical conditions. Current medical condition will be summarized as well separately.

Ocular events will be presented separately for the study eye and fellow eye.

Data will be tabulated using primary system organ class (SOC) and preferred term (PT) according to the MedDRA dictionary V20.1.

Data collected on the Medical History eCRF for the extension study will be listed for both treatment groups. Columns will be included to identify if the event started before the core study, during the core study, during the transition period or during the extension study and if the event is ongoing or ended during the transition period or during the extension study.

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

Descriptive analyses and listings will be presented for the brolucizumab treatment group. Data for the aflibercept treatment group will be presented in listings.

2.4.1 Study treatment / compliance

Extent of exposure to study treatment is calculated as the number of injections received. The following summaries will be presented:

- Overall number of treatments from extension baseline to exWeek 24 using the following categories: active and sham, active only, sham only
- Treatment exposure by visit: The number and percent of patients who received active injections, sham injections, missed a treatment (active and sham) and missed visits will be presented by visit and by treatment status (q8, q12)
- Frequency of all observed dosing patterns from extension baseline to exWeek 24 differentiating between active and sham treatments, missed treatments and wrong treatments
- brolucizumab q12/q8 allocation by visit: Number and percent of patients on q12 and q8 at each visit, including number of patients switched from q12 to q8

Exposure data will be listed for both treatment groups.

2.4.2 Prior, concomitant and post therapies

The following describes the data to be recorded on the extension study eCRFs.

Medications

For patients where Core end of study visit date and Extension study first visit date occur on the same day the following data is recorded on the Concomitant Medications eCRF:

a) Medications started on Core end of study visit date/Extension study first visit date
b) Medications taken at least once during the Extension Study

For patients where Core end of study visit date and Extension study first visit date do not occur on the same day the following data is recorded on the Concomitant Medications eCRF:

c) Medications started during the core study and stopped during the transition period
d) Medications started during the core study and ongoing at Extension study first visit date
e) Medications started and stopped during the transition period
f) Medications started during the transition period and ongoing at Extension study first visit date

Procedures

For patients where Core end of study visit date and Extension study first visit date occur on the same day the following data is recorded on the Procedures eCRF:

a) Procedures occurring on date of Core end of study visit date/Extension study first visit date
b) Procedures occurring during the Extension Study

For patients where Core end of study visit date and Extension study first visit date do not occur on the same day, the following data is recorded on the Procedures eCRF:

a) Procedures occurring during the Extension Study

Note: Procedures occurring during the transition period are recorded on the Medical History eCRF.

2.4.2.1 Prior medications

Prior medications (ocular and non-ocular) will be summarized using number and percent of patients by ATC class and preferred term according to the WHO Drug reference list dictionary.

Prior ocular medications will be summarized separately for the study eye and fellow eye.

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

Prior medications will be listed for both treatment groups.

2.4.2.2 Prior surgical and medical procedures

Prior surgical and medical procedures (ocular and non-ocular) will be summarized using number and percent of patients by primary system organ class and preferred term according to the MedDRA dictionary V20.1.

Prior ocular surgical and medical procedures will be summarized separately for the study eye and fellow eye.

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

Prior surgical and medical procedures will be listed for both treatment groups.

2.4.2.3 Concomitant medications

Concomitant medications (ocular and non-ocular) will be summarized using number and percent of patients by ATC class and preferred term according to the WHO Drug reference list dictionary.

Concomitant ocular medications will be summarized separately for the study eye and fellow eye.

A concomitant medication is defined as any medication taken at least once after the first injection of study treatment in this extension study.

Concomitant medications will be listed for both treatment groups.

2.4.2.4 Concomitant surgical and medical procedures

Concomitant surgical and medical procedures (ocular and non-ocular) will be summarized using number and percent of patients by primary system organ class and preferred term according to the MedDRA dictionary V20.1.

Concomitant ocular surgical and medical procedures will be summarized separately for the study eye and fellow eye.

Concomitant surgical and medical procedures are those that occurred after the date of the first injection of study treatment in this extension study.

Concomitant surgical and medical procedures will be listed for both treatment groups.

2.5 Analysis of safety and efficacy variables

Analyses and listings will be presented for the brolucizumab treatment group. Data for the aflibercept treatment group will be presented in listings.

2.5.1 Safety and efficacy variables

Safety and efficacy variables are:

- Treatment emergent Adverse Events
- Best-corrected visual acuity
- q12 treatment status at exWeek 24
- Anti-drug antibodies, including drug exposure
- Central Subfield Thickness
- Intraocular pressure
- Vital signs

2.5.2 Statistical hypothesis, model, and method of analysis

Formal hypothesis testing is not planned for this study.

2.5.2.1 Efficacy variables

Best-Corrected Visual Acuity

BCVA will be analyzed for the study eye. BCVA data for both the study eye and fellow eye will be listed for both treatment groups.

The following summaries will be presented:

- The number and percentage with a loss in BCVA ≥5, ≥10, ≥15, ≥ 30 letters from exBL to each post-exBL study visit
- The number and percentage with a gain in BCVA ≥5, ≥10, ≥15 letters from exBL to each post-exBL study visit

Note: Patients with BCVA value of 84 letters or more at a post-baseline visit will be considered as responders for the corresponding endpoint. This is to account for a ceiling effect, e.g. for the' ≥15-letter gain' endpoint, for those patients with BCVA values at baseline ≥ 70 letters.

- Descriptive statistics for change from exBL in BCVA to each post-exBL study visit and coWeek 96 visit.

BCVA assessments after start of alternative anti-VEGF treatment in the study eye will be censored and imputed by the last value prior to start of this alternative treatment. See Section 2.5.3 for further details of the last observation carried forward (LOCF) rules to be used to impute censored or missing BCVA values.

See Section 2.5.4.1 for details of the sensitivity analyses which will be performed for the above BCVA endpoints.

Using the core study data, descriptive statistics for change from coBL in BCVA (LOCF) to each post-baseline study visit for patients included in the Extension Safety Set will be summarized by core study treatment group (brolucizumab 3 mg, brolucizumab 6 mg) and pooled. This will be repeated for BCVA without imputation with LOCF (with censoring) of BCVA data after start of alternative anti-VEGF treatment in the study eye.

Means and standard errors (SE) for change in BCVA (LOCF) for the study eye will be presented graphically by study visit for the 96 week core study treatment period and the 24 week extension study treatment period. Core study data will be plotted together with extension study data by core study treatment group.

Using the core study data, summary statistics will be displayed for the average change in BCVA from core Week 68 (coWeek 68) to Week 84 through Week 96 in the core study, the average change in BCVA from exBL to Week 12 through Week 24 in the extension study and for the difference (with 95% confidence interval). In addition, average change in BCVA from coWeek 68 to coWeek 84 through coWeek 96 vs the average change in BCVA from exBL to exWeek 12 through exWeek 24 will be displayed using a shift table with categories: ≤ -15, >-15 to <-10, ≥-10 to <10, ≥10 to <15, ≥ 15 letters. The analysis will be conducted 1) with censoring of BCVA assessments after start of alternative anti-VEGF treatment in the study eye and censored or missing BCVA values imputed with LOCF and 2) with censoring of BCVA assessments after start of alternative anti-VEGF treatment in the study eye but without imputation with LOCF of missing or censored values.

q12 treatment status at exWeek 24

The proportion of patients with a positive q12 treatment status at Week 24 will be presented. Patients without an identified q8 need (according to the investigator's disease activity assessment (DAA)) at exWeek 16 and exWeek 20 are considered to have a positive q12 status at exWeek 24.

The estimate for the proportion of patients with a positive q12 treatment status at Week 24 will be derived from Kaplan Meier time-to-event analyses for the event 'first q8-need' applying a 'q8-need' allocation in case of missing or confounded data attributable to lack of efficacy and/or lack of safety and censoring as described below.

The proportion of patients with a positive q12 treatment status will be derived as follows requiring 'duration of effect' (as assessed by q8 need) together with 'sufficient efficacy and safety':

- For the 'duration of effect' requirement patients will need to have the status of 'q8 need = no' at exWeek 16 and exWeek 20 unless the 'q8 need = yes' is confounded by reasons other than lack of efficacy and/or safety (see censoring details below).
- The requirement regarding 'sufficient efficacy and safety' will be addressed by considering patients – even without an explicit 'q8 need = yes' – as having a negative q12 status in case any of the following confounding factors is attributable to lack of efficacy and/or lack of safety of the study treatment (assessed based on a masked medical review, see Section 5.3 for further details): early treatment/study discontinuation, use of forbidden concomitant medications/procedures and/or other deviation from treatment schedule (e.g. due to a missed visit/treatment). The corresponding q8 need will be allocated to the next DAA visit (according to the protocol) following the occurrence of such a confounding factor.

  In case the missing or confounded data regarding the q12 treatment status are attributable to reasons other than lack of efficacy and/or safety, the patient is censored within the q12 treatment status according to the following specifications:

  - Early treatment/study discontinuation: Censoring at the last valid DAA.
  - Single missed visit with a relevant DAA: Censoring at the last valid DAA prior to the missed visit.
  - Prohibited concomitant medications/procedures: Censoring at the last valid DAA prior to the corresponding application.
  - Discrepancy between DAA by investigator and the actual treatment received: Censoring at the visit of the discrepancy (assuming the DAA is valid).
  - Other treatment allocations/applications deviating from the concept of 'disease activity'. Censoring at the last valid DAA at or prior to the deviation.

Remark: Patients without any relevant valid DAA are considered censored at extension baseline.

The proportion of patients with a positive q12 treatment status at exWeek 24 will be displayed by q12 treatment status at coWeek 96 and by core study treatment group (brolucizumab 6 mg, brolucizumab 3 mg).

Central Subfield Thickness

The change in CSFT from exBL to each post-exBL study visit will be summarized descriptively for the study eye. CSFT assessments after start of alternative anti-VEGF treatment in the study eye will be censored and imputed by the last value prior to start of this alternative treatment. See Section 2.5.3 for further details regarding the LOCF rules to be used to impute missing CSFT values.

CSFT data for the study eye and fellow eye will be listed for both treatment groups.

See Section 2.5.4.1 for details of the sensitivity analysis which will be performed for CSFT.

Using the core study data, change in CSFT (LOCF) for the study eye for patients included in the Extension Safety Set will be summarized by study visit and core study treatment group (brolucizumab 3 mg, brolucizumab 6 mg) and pooled. This will be repeated for CSFT without imputation with LOCF of CSFT data after start of alternative anti-VEGF treatment in the study eye.

Means and SEs for change in CSFT (LOCF) for the study eye will be presented graphically by study visit for the 96 week core study treatment period and the 24 week extension study treatment period. Core study data will be plotted together with extension study data by core study treatment group.

Using the core study data, summary statistics will be displayed for the average change in CSFT from coWeek 68 to coWeek 84 through coWeek 96, the average change in CSFT from exBL to exWeek 12 through exWeek 24 and for the difference (with 95% confidence interval). In addition, average change in CSFT from coWeek 68 to coWeek 84 through coWeek 96 in the core study vs the average change in CSFT from exBL to exWeek 12 through exWeek 24 in the extension study will be displayed using a shift table with categories: ≤ -100, > -100 to < -50, ≥ -50 to <50, ≥ 50 to < 100, ≥ 100 µm. These analyses will be conducted 1) with censoring of CSFT assessments after start of alternative anti-VEGF treatment in the study eye and censored or missing CSFT values imputed with LOCF and 2) with censoring of CSFT assessments after start of alternative anti-VEGF treatment in the study eye but without imputation with LOCF of missing or censored values.

2.5.2.2 Safety variables

Safety analyses will include all treatment emergent data, including data collected after the patient discontinued study treatment and started alternative anti-VEGF treatment. See Section 2.5.4.2 for details of the sensitivity analyses which will be performed for safety variables.

Ocular and non-ocular findings (e.g. AEs) will be presented separately. All results related to ocular assessments will be presented using data from the study eye only, except for AEs where summaries will be presented separately for both the study eye and fellow eye.

Treatment emergent Adverse Events

The following describes the data to be recorded on the extension study eCRFs.

For patients where Core end of study visit date and Extension study first visit date occur on the same day the following data are recorded on the Adverse Event eCRF:

a) Events started during the core study and and ongoing at Extension study first visit date
b) Events occurring during the Extension Study

For patients where Core end of study visit date and Extension study first visit date do not occur on the same day the following data is recorded on the Adverse Event eCRF:

a) Events started during the core study and ongoing at Extension study first visit date
b) Events occurring during the Extension Study

Note that AEs which start during the core study and end during the transition period are recorded on the Medical History eCRF not the Adverse Event eCRF. Therefore these events are not included in any AE summaries or listings but will be included in Medical History listings.

The study protocol states that, for each patient, AEs are collected after written informed consent for participation in the study has been provided until the end-of-study visit.

Treatment emergent AEs are defined as AEs which start on or after the time of the first injection of study treatment in this extension study and until the patient exits the study.

For treatment emergent AE analyses, separate summaries will be produced for ocular and non-ocular events. Ocular events will be presented for the study eye and fellow eye separately. MedDRA Dictionary V20.1 will be used.

The number and percentage of patients who report treatment emergent AEs will be summarized by primary SOC and PT.

In addition, the following treatment emergent AE summaries will be presented using number and percent of patients:

- SAEs by primary SOC and PT
- AEs by maximum severity, primary SOC and PT
- AEs resulting in treatment and/or study discontinuation by primary SOC and PT
- AEs of potential relevance to intravitreal anti-VEGF class PT (according to the RTH258 nAMD electronic case retrieval strategy (eCRS) at the time of the core study CRTH258-C001 clinical database lock)
- AEs by causal relationship to study treatment and ocular injection procedure by primary SOC and PT

Treatment emergent AEs will be listed for both treatment groups.

See Section 2.5.4.2 for details of the sensitivity analyses which will be performed for treatment emergent AEs.

AEs which start prior to the date/time of the first injection of study treatment in this extension study will be summarized using number and percent of patients by primary SOC and PT. Prior AEs will be listed for both treatment groups.

Treatment emergent deaths will be summarized using counts and percentages by primary SOC and PT.

All deaths including date and cause of death will be listed for both treatment groups.

AEs occurring during the last 6 months of the core study (defined as events with a start date on or after the date of core study Visit 19 /Week 68), for the patients included in the Extension Safety Set will be presented by core study treatment group (brolucizumab 3 mg, brolucizumab 6 mg) using number and percent of patients. CoWeek 68 was chosen to consider the period between coWeek 68 and coWeek 96 as the last 6 months of the core study (actually 28 weeks) in order to reflect a similar exposure between brolucizumab patients since all of them were planned to receive 3 active injections during the period coWeek 68 to coWeek 96.

The number and percentage of patients presenting AEs during the extension study and during the last 6 months of the core study will be displayed as well. The following summaries will be presented:

- AEs by primary SOC and PT
- SAEs by primary SOC and PT
- AEs by maximum severity, primary SOC and PT
- AEs resulting in treatment and/or study discontinuation by primary SOC and PT
- AEs of potential relevance to intravitreal anti-VEGF class by category of events (according to the RTH258 nAMD eCRS at the time of the CRTH258-C001 clinical database lock)
- AEs of potential relevance to intravitreal anti-VEGF class by category of events by AE status during the core study (present, absent, ongoing) vs AE status during the extension study (present, absent, ongoing).

  Note:

  1. Core study AE status = "ongoing" means that the AE was ongoing at coWeek 68. However, if a patient has an AE which is ongoing at coWeek 68 and this AE subsequently ends during the core study but then occurs again during the last 6 months of the core study, this patient is counted under AE status during core study = "present" ("present" status supersedes "ongoing" status).
  2. Extension study AE status = "ongoing" means that the AE was ongoing on the date of first injection of study treatment in the extension study (exBL). However, if a patient has an AE which is ongoing on the date of first injection of study treatment in the extension study and this AE subsequently ends during the extension study but then occurs again during the extension study, this patient is counted under AE status during the extension study = "present" ("present" status supersedes "ongoing" status.
- AEs by causal relationship to study treatment and ocular injection procedure by primary SOC and PT

Best-Corrected Visual Acuity

Counts and percentages of patients with a loss in BCVA ≥5, ≥10, ≥15, ≥ 30 letters from exBL to each post-exBL study visit, and maximum loss at any visit will be presented.

A listing of all patients with a ≥15 letter loss in BCVA from extension baseline to any post-baseline visit will be presented.

Anti-drug antibodies [redacted]

ADA status is defined using the following criteria:

- ADA negative:
  - ADA negative at all time points (pre-dose and post-dose)
  - ADA negative at pre-dose and no titer values above 10 at all other time points

- ADA titer of 10 at pre-dose but negative at all other time points

- ADA positive without boost:
  - ADA positive at pre-dose, post-dose titer values do not increase from pre-dose by more than 3-fold (1 dilution) at any time point
- Induced:
  - ADA negative at pre-dose, post-dose titer value of 30 or more increase
- Boosted:
  - ADA positive at pre-dose, post-dose titer values increase from pre-dose by more than 3-fold (1 dilution) at any time point

The ADA titer value will be presented by visit. The number and percent of patients induced or boosted according to their integrated ADA status will be presented.

[redacted]

Intraocular pressure

Pre-injection IOP and changes from extension baseline will be summarized descriptively by study visit. Post-injection IOP will be summarized descriptively by study visit and by injection type (active, sham).

Summary tables with counts and percentage of patients with an IOP increase of ≥10, ≥20mmHg from pre-injection to post-injection will be presented by study visit, at the last visit, and at any visit. In addition, the number and percentage of patients with a post-injection IOP > 30mmHg will be presented by study visit, at the last visit and at any visit. The IOP assessment performed at approximately 30 minutes post-injection will be used for these summaries.

A summary table with counts and percentage of patients with a pre-injection IOP ≥ 21mmHg in 3 consecutive scheduled visits will be presented. This will be repeated for patients with a post-injection IOP ≥ 21mmHg in 3 consecutive visits. In addition, the number and percentage of patients with a pre-injection IOP > 30mmHg will be presented by study visit, at the last visit and at any visit.

IOP data will be listed for both treatment groups. In addition, a listing for patients with any post-injection IOP increase of ≥10mmHg from pre-injection IOP and a listing of patients with any IOP > 30mmHg will be presented.

Vital signs

Descriptive summaries of observed values and change from extension baseline to each study visit in each vital sign parameter will be presented.

A summary table with number and percentage of patients with clinically notable findings (see Table 2-1) will be presented by study visit, at the last visit and at any visit.

Table 2-1 Clinically notable changes in vital signs

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

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

A listing of all vital sign parameters will be presented for both treatment groups. In addition, a separate listing for patients satisfying at least one criterion in Table 2-1 will also be presented.

2.5.3 Handling of missing values/censoring/discontinuations

For the efficacy variables, BCVA and CSFT, missing data will be imputed using LOCF. Observed values from both scheduled and unscheduled study visits will be used for the LOCF imputation. For patients with no post-exBL value, no imputation will be performed.

For patients who discontinue treatment but continue in the study, the efficacy data will be censored at the time the patient started alternative anti-VEGF treatment in the study eye. Start date of an alternative anti-VEGF treatment will be identified using the Concomitant Medication eCRF where Standardized Medication Name (SAS variable name = CMDECOD) = "RANIBIZUMAB", "AFLIBERCEPT", "BEVACIZUMAB" or "PEGAPTANIB". No other censoring is applied. Censored or missing data will be imputed by the last observation prior to receiving alternative anti-VEGF treatment.

Details regarding handling of missing values and discontinuations including the timing of censoring within the time-to-event analysis of the proportion of patients with a positive q12 treatment status at exWeek 24 are specified in Section 2.5.2.1.

2.5.4 Sensitivity analyses

2.5.4.1 Efficacy variables

Best-Corrected Visual Acuity

Descriptive statistics for change from exBL in BCVA to each post-exBL study visit (and coWeek 96 visit).

- With censoring of BCVA assessments after start of alternative anti-VEGF treatment in the study eye. No imputation with LOCF will be applied.

All BCVA values (as imputed, as observed, as censored) will be listed.

Central Subfield Thickness

The change in CSFT from extension baseline to each post-baseline study visit will be summarized descriptively for the study eye with censored CSFT assessments after start of alternative anti-VEGF treatment in the study eye. No imputation with LOCF will be applied.

All CSFT values (as imputed, as observed, as censored) will be listed.

2.5.4.2 Safety variables

Treatment emergent Adverse Events

The following sensitivity analyses, will be conducted, in which, for patients who discontinue treatment but continue in the study, with application of alternative anti-VEGF treatment, their safety data are censored at the time the patient starts alternative anti-VEGF treatment. That is, only safety data collected prior to receiving alternative anti-VEGF treatment will be used for these analyses (see Section 2.5.3 for further details regarding the identification of start date of alternative anti-VEGF treatment). Using number and percentage of patients the following summaries will be presented:

- Treatment emergent AEs by primary SOC and PT
- Treatment emergent SAEs by primary SOC and PT

Separate summaries will be produced for ocular and non-ocular events. Ocular AEs will be presented for the study eye and fellow eye separately.

Additionally, for patients who received alternative anti-VEGF treatment, a listing of treatment emergent AEs for AEs with a start date after the patient received alternative anti-VEGF treatment will be presented by primary SOC and PT. This will be repeated for SAEs.

2.6 Interim analysis

This analysis plan assumes that no IA will be performed.

3 Sample size calculation

Approximately 75 to 100 patients who completed study CRTH258-C001 are expected to be enrolled in this study. This sample size is not based on a power calculation and depends on the number of patients in the core study fulfilling the eligibility criteria of the extension study.

4 Change to protocol specified analyses

- The protocol defined extension baseline as the value at Day 1. The definition has been changed to be “the last available value collected prior to the first treatment”.
- The protocol defined that AEs would be summarized by safety topic of interest and preferred term using the eCRS. Text has been added into this SAP to clarify that the eCRS to be used is the RTH258 nAMD eCRS at the time of the CRTH258-C001 clinical database lock.

- Overall number of treatments will be presented for the entire extension period but not by time period

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

5.1.1.1 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.

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

5.1.1.2 AE start date imputation

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

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

The following matrix explains the logic behind the imputation.

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

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

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

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a

rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.

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

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

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

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

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

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

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

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

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

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

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

5.1.2 Concomitant medication date imputation

5.1.2.1 Concomitant medication (CM) end date imputation

1. If the CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date is set to NULL.
2. Else, if the CM end date month is missing, the imputed end date should be set to the earliest of the (treatment end date, 31DECYYYY, date of death).
3. If the CM end date day is missing, the imputed end date should be set to the earliest of the (treatment end date, last day of the month, date of death).

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

5.1.2.2 Concomitant medication start date

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.

5.1.2.3 Medical history date of diagnosis imputation

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

- If DIAG year < treatment start date year and DIAG month is missing, the imputed DIAG date is set to the mid-year point (01JULYYYY)
- else if DIAG month is not missing, the imputed DIAG date is set to the mid-month point (15MONYYYY)

- If DIAG year = treatment start date year
  - and (DIAG month is missing OR DIAG month is equal to treatment start month), the imputed DIAG date is set to one day before treatment start date
  - else if DIAG month < treatment start month, the imputed DIAG date is set to the mid-month point (15MON YYYY)
  - else if DIAG month > treatment start month => data error

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

5.2 Rules for exclusion from the Extension Safety Set

Protocol deviations are defined in the Protocol Deviations Requirements Document. Table 5-1 includes the protocol deviations which lead to exclusion of a patient from the Extension Safety Set:

Table 5-1 Protocol deviations leading to exclusion from the extension safety set

Deviation ID	Description of Deviation	Exclusion in Analyses
TRT01	Enrolled but no study drug administered during the extension study	Exclude from Extension Safety Set

5.3 Censoring rules for analysis of q12 treatment status at exWeek 24

For the analysis of q12 treatment status at exWeek 24, Analysis Restrictions (ARs) will address the limitations in the patient's evaluability resulting from missing or confounded data with an underlying background not qualifying as a PD, i.e. early study terminations, early treatment discontinuations, missed visits /treatments /assessments.

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)
- Lack of safety/tolerability of the study treatment (= 2)
- Other (= 0)

The focus of the ARs is the identification of censoring related to the analysis of the q12 proportion as derived from DAA and described in Section 2.5.2.1. Censoring is only applied in case the underlying reason for a confounded DAA is assessed as '0'.

ARs will be identified at the patient level by masked team members before DBL.

The following rules apply for handling missed injections/visits during the study (Unmasked Clinical Scientific Expert will perform AR/PD review and will present in masked fashion to masked clinical team to ensure appropriate PD or AR allocation):

a. If a patient missed sham injection → not a PD or AR.

b. If a patient missed active treatment due to an AE related to study drug or study procedure with action taken "drug interrupted" or "drug withdrawn" → not a PD but an AR.

c. If a patient missed active treatment due to AE not related to study drug or study procedure (e.g. fall and fractured hip) but which prevented the study visit from occurring, or had an ocular AE determined unrelated to study treatment / procedure but which prohibited safe administration of study treatment (e.g. blepharitis) → not a PD but an AR.

d. If a patient missed active treatment due to any other reason → a PD.

e. Allocation of AR codes for early treatment discontinuations and early study discontinuations will be based on a totality of available patient data.

The following tables specify for all relevant protocol specifications and study assessments the criteria to be used for establishing whether a protocol deviation or analyis restriction has occurred and, if applicable, whether the AR has an effect on analysis (censoring for DAA).

The Table 5-3 also highlights whether the PD is identified by the masked or unmasked study personnel.

Table 5-2 Analysis Restrictions (ARs)

Analysis restriction (AR)	Description of AR code	Censoring of DAA	Reason 0=other 1=LoE 2=LoS	Comment
AR_EST_01	Early study termination due to lack of efficacy	0	1	Early termination reason = lack of efficacy. Temporal mapping: first corresponding missed visit
AR_EST_02	Early study termination due to lack of safety	0	2	Early termination reason= AE; AE reviewed by clinical regarding link to treatment (lack of efficacy / safety) Temporal mapping: first corresponding missed visit
AR_EST_03	Early study termination due to reasons other than lack of efficacy / safety	0	0	Temporal mapping: first corresponding missed visit
AR_ETD_01	Early treatment discontinuation due to lack of efficacy	0	1	Early discontinuation reason = lack of efficacy. Temporal mapping: first visit following the decision to stop treatment. Missed treatments at the visit of decision are captured via an AR_TRT05 code. Remark: regarding the final DA status see Section 2.5.2.1
AR_ETD_02	Early treatment discontinuation due to lack of safety	0	2	Early discontinuation reason= AE; AE reviewed by clinical regarding link to treatment (lack of efficacy / safety) Temporal mapping: first visit following the decision to stop treatment. Missed treatments at the visit of decision are captured via an AR_TRT05 code. Remark: regarding the final DA status see Section 2.5.2.1

Analysis restriction (AR)	Description of AR code	Censoring of DAA	Reason 0=other 1=LoE 2=LoS	Comment
AR_ETD_03	Early treatment discontinuation due to reasons other than lack of efficacy / safety	0	0	Temporal mapping: first visit following the decision to stop treatment. Missed treatments at the visit of decision are captured via an AR_TRT05 code. Case by case: Based on potential treatment patterns including the 'q8-need' status it is assessed up to which visit the patient at minimum is treated as per protocol. Remark: there are no DAA after treatment discontinuation.
AR_TRT_05	Missed active treatment for reasons other than lack of efficacy or related safety event or PD (=TRT05)	3	0	Temporal mapping: first corresponding missed visit
AR_TRT_05_S	Missed active treatment for related safety event	0	2	Temporal mapping: first corresponding missed visit
AR_TRT_05_E	Missed active treatment due to lack of efficacy	0	1	Temporal mapping: first corresponding missed visit

For Reason in above table: LoE = lack of efficacy; LoS = lack of safety

*Censoring: 0=no censoring, 1=exclusion of value at PD visit, 2=censoring at visit preceding PD visit (exclusion of values from all visits starting from PD visit), 3=censoring at PD visit (exclusion of values from all visits following the PD visit)

Table 5-3 Protocol Deviations (PDs)

PD ID (Code)	Description of the ID Code	PD Category Description	Censoring of DAA	Reason 0=other 1=LoE 2=LoS	Comment
INCL01	Study ICF not obtained prior to study related procedure(s) performed	Selection criteria not met	0	0	
INCL02	Pregnancy ICF not obtained prior to study related procedure(s) performed	Selection criteria not met	0	0	
INCL03	Patient entered the study > 12 weeks after completion of the core study	Selection criteria not met	0	0	
EXCL01	Patient discontinued the core study prematurely	Selection criteria not met	0	0	
EXCL02	Patient discontinued the treatment in the core study prematurely	Selection criteria not met	0	0	
EXCL03	Patient received standard of care medication for nAMD in the study eye after completion of the core study	Selection criteria not met	0	0	
EXCL04	Patient received investigational treatment for nAMD in the study eye after completion of the core study	Selection criteria not met	0	0	
EXCL05	Patient received intraocular or periocular injection of steroids in the study eye after completion of the core study	Selection criteria not met	0	0	
EXCL06	Patient received systemic anti-VEGF therapy after completion of the core study	Selection criteria not met	0	0	

PD ID (Code)	Description of the ID Code	PD Category Description	Censoring of DAA	Reason 0=other 1=LoE 2=LoS	Comment
EXCL07	Patient has a systemic or ocular medical condition or personal circumstance precluding study participation or compliance with study procedures	Selection criteria not met	0	0	
EXCL08	Patient had a stroke or myocardial infarction within 3 months of Baseline visit	Selection criteria not met	0	0	
EXCL09	Patient participated in an investigational drug, biologic, or device study within 30 days or 5 half-lives of the investigational drug prior to entering the extension	Selection criteria not met	0	0	
EXCL10	Female patient was pregnant or nursing (lactating) at Baseline	Selection criteria not met	0	0	
EXCL11	Female patient of child bearing potential and not using an effective method of contraception	Selection criteria not met	0	0	
TRT01	Patient enrolled but no study drug administered	Treatment allocation	0	0	
TRT02	Patient received wrong study drug	Treatment allocation	3	0	
TRT03	Patient received active treatment when schedule was for sham	Treatment allocation	0/3 (3 in relation to the second TRT03)	0	
TRT04	Patient did not have disease activity but received active treatment	Treatment allocation	3	0	Overtreatment
TRT05	Patient missed active treatment for reasons other than lack of efficacy or any safety event	Treatment allocation	3	0	

PD ID (Code)	Description of the ID Code	PD Category Description	Censoring of DAA	Reason 0=other 1=LoE 2=LoS	Comment
TRT06	Patient received sham when schedule was for active treatment	Treatment allocation	3	0	Undertreatment
TRT07	Patient received over-dose of study treatment at a single visit	Treatment allocation	0	0	
TRT08	Patient was injected in the wrong eye (i.e. not "study eye")	Treatment allocation	0	0	
OTH02	Masked personnel unmasked to study treatment assignment without subsequent involvement in efficacy assessments (BCVA and/or DAA)	Other	0	0	
OTH03	Patient potentially unmasked	Other	3	0	
OTH04	Unmasked personnel performed efficacy assessments	Other	2	0	
OTH05	BCVA in the study eye not performed correctly	Other	0	0	
OTH06	Pregnancy testing not performed	Other	0	0	
OTH07	ADA and/or systemic RTH258 testing not drawn prior to injection	Other	0	0	
OTH08	Sham injection given with a needle	Other	0	0	
OTH09	Injection administered although subject had active ocular or periocular infection and/or active intraocular inflammation	Other	0	0	
OTH10	Injection procedure performed with potential risk to patient	Other	0	0	
COMD01	Prohibited ocular medication and/or procedure in the study eye	Conc. medication	3	0	

PD ID (Code)	Description of the ID Code	PD Category Description	Censoring of DAA	Reason 0=other 1=LoE 2=LoS	Comment
COMD02	Prohibited systemic medication	Conc. medication	0	0	
COMD03	Investigational treatment in nonstudy eye	Conc. medication	0	0	
WITH01	Patient became pregnant during the study but study treatment was not discontinued	Withdrawal	0	0	
WITH02	Patient received anti-VEGF therapy in the study eye other than the IP but study treatment was not discontinued	Withdrawal	0	0	
WITH03	Patient received intraocular or periocular injections of corticosteroids in the study eye but study treatment was not discontinued	Withdrawal	0	0	
WITH04	Patient received laser treatment for AMD in the study eye but study treatment was not discontinued	Withdrawal	0	0	
WITH05	Patient received systemic anti-VEGF but study treatment was not discontinued	Withdrawal	0	0	
WITH06	Patient received any systemic investigational drug, biologic or device but study treatment was not discontinued	Withdrawal	0	0	
WITH07	The emergency unmasking has been done but study treatment was not discontinued	Withdrawal	0	0	

For Reason in above table: LoE = lack of efficacy; LoS = lack of safety

*Censoring: 0=no censoring, 1=exclusion of value at PD visit, 2=censoring at visit preceding PD visit (exclusion of values from all visits starting from PD visit), 3=censoring at PD visit (exclusion of values from all visits following the PD visit)