Clinical Development

RTH258/Brolucizumab

RTH258A2301 (HAWK) / NCT02307682

A Two-Year, Randomized, Double-Masked, Multicenter, Three-Arm Study Comparing the Efficacy and Safety of RTH258 versus Aflibercept in Subjects with Neovascular Age-Related Macular Degeneration

Statistical Analysis Plan (SAP)

Author: [redacted]

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24-Feb-2017	Prior to DB lock	Creation of final version	*NIA* First version (V1.O) approved in documentum system.	*NIA*
12-June-2017	Prior to DB lock	Creation of amendment-I • futroduction of additional hypotheses testing in relation to secondaiy endpoints • Adjustments in relations to observed protocol deviations and analysis restrictions, e.g. detailed specifications for the per-protocol set including censoring and the assessment of the q12 proportion based on a time-to-event analysis • [redacted] • Addition of "AEs of potential relevance to intravitrealanti-VEGF class" under "Adverse events (AEs)" sub-section (2.8.2)	Updated.	Sub-sections 1.2, 2.2, 2.4, 2.5. 2.6, 2.7, 2.8 and 5

List of abbreviations

AE	Adverse event
AR	Analysis Restrictions
nAMD	Neovascular Age-related Macular Degeneration
BCVA	Best Corrected Visual Acuity
CI	Confidence Interval
CNV	Choroidal Neovascularization
CSFT	Central Subfield Thickness
CSFTns	Central Subfield Thickness-neurosensory retina
CSFTtot	Central Subfield Thickness-total
CSM	Clinical Site Management
CSR	Clinical Study report
CTM	Clinical Trial Management
DA	Disease Activity
DEP	Deviations and Evaluability Plan
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
IOP	Intraocular Pressure
IP	Investigational Product
IVR	Interactive Voice Response
IVT	Intravitreal
LSM	Least Squares Mean
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NMQ/CMQ	Novartis MedDRA Query/Custom Novartis MedDRA Query
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
q8	Treatment every 8 weeks
q12	Treatment every 12 weeks
QoL	Quality of Life
RAP	Retinal Angiomatous Proliferation
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
SE	Standard Error
SOC	System Organ Class
SoC	Standard of Care
TFLs	Tables, Figures, Listings
VA	Visual Acuity
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of statistical analysis planned in the study protocol, and to provide detailed statistical methods that will be used for the Clinical Study Report (CSR) of study RTH258A2301.

Data will be analyzed according to the data analysis Section 11 of the study protocol which will be available in Appendix 16.1.1 of the CSR. Important information is given in the following sections and details will be provided, as applicable, in Appendix 16.1.9 of the CSR.

The SAP will be finalized before treatment unmasking. Any changes to the SAP after approval will be documented.

1.1 Study design

This is a prospective, randomized, double masked, multicenter, three arm study comparing the efficacy and safety of RTH258 intravitreal (IVT) injections versus aflibercept IVT injections in subjects with neovascular age-related macular degeneration (AMD).

The three treatment arms are:

Arm 1: Brolucizumab 3 mg/50 µL (a.k.a RTH258 3 mg/50 µL)

Arm 2: Brolucizumab 6 mg/50 µL (a.k.a RTH258 6 mg/50 µL)

Arm 3: Aflibercept 2 mg/50 µL (a.k.a Eylea 2 mg/50 µL)

Subjects in all the three arms will have visits every 4 weeks through Week 96.

According to protocol, approximately 330 subjects per arm (total 990 subjects) will be randomized in this trial. More details of the sample size calculation can be found in Section 3. By the time this first amendment is implemented, 1,082 subjects were randomized in the study.

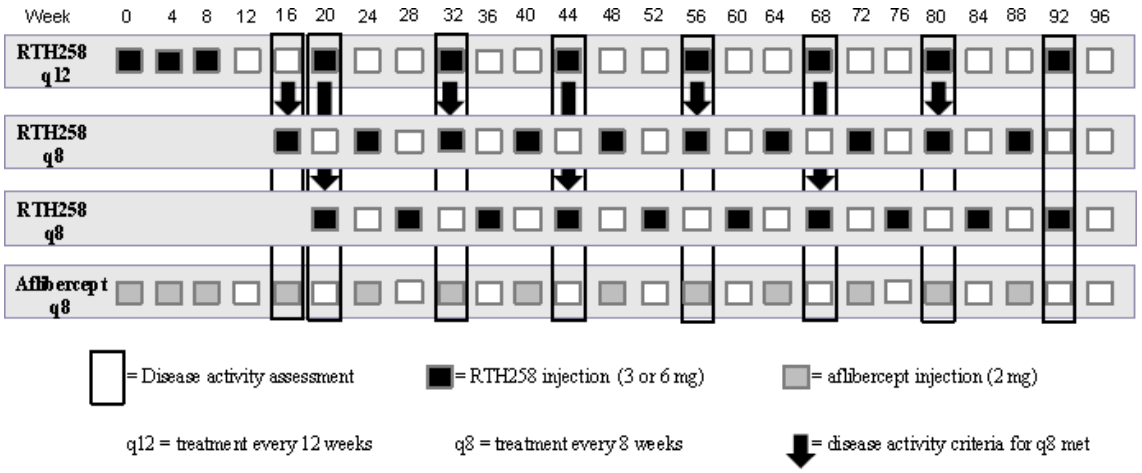
Subjects in the RTH258 3 mg (Arm 1) and RTH258 6 mg (Arm 2) will be initially injected 3 times at 4 week intervals, at Visit 1/Baseline, Visit 2/Week 4 and Visit 3/Week 8.

Following these 3 loading doses, each subject will be injected every 12 weeks (q12) up to Visit 25/Week 92 unless there is disease activity assessed according to the guidance provided at Visit 6/Week 16, Visit 7/Week 20, Visit 10/Week 32, Visit 13/Week 44, Visit 16/Week 56, Visit 19/Week 68, Visit 22/Week 80 or Visit 25/Week 92. If disease activity is identified, the subject will be reassigned to receive injections every 8 weeks (q8) thereafter, up to Week 88/92. Refer to protocol Section 10.1 for disease activity criteria.

In Arm 3, aflibercept 2 mg, (EYLEA®, comparator) will be injected 3 times at 4 week intervals (Visit 1/Baseline, Visit 2/Week 4 and Visit 3/Week 8), followed by injections every 8 weeks (q8) up to Visit 24/Week 88.

The dosing schedule by treatment is presented graphically below.

Figure 1 Dosing schedule by treatment



1.1.1 Randomization

A member of the Statistical Programming group at Alcon who is not part of the study team will generate the randomized allocation for the study treatment assignment based on a randomization plan providing study specific criteria for randomization including block size and randomization ratio. Treatment is assigned to subjects through the Interactive Response Technology (IRT) system. Each subject number is associated with a treatment group according to the randomized allocation generated using the computer software SAS version 9.2 PROC PLAN. Subjects are assigned subject identification numbers sequentially according to time of randomization.

Eligible subjects will be randomized at visit 1/Baseline centrally using Interactive Response Technology (IRT) in a 1:1:1 ratio to receive either RTH258 3 mg/50 µL, RTH258 6 mg/50 µL, or aflibercept 2 mg/50 µL. Randomization for subjects in Japan will be stratified according to presence or absence of polypoidal choroidal vasculopathy (PCV). PCV is identified at the screening visit using indocyanine green (ICG) imaging and confirmed by the Central Reading Center (CRC). The randomization schedule will be blocked to ensure a balance of treatment allocations across the study.

1.1.2 Masking

This is a double–masked study. The investigator, investigator staff (except for the unmasked site personnel and unmasked injecting physician), subjects and Sponsor personnel (except for those who have been delegated responsibility for working with the IP) involved with conduct of the trial are masked with regard to treatment assignment while the study is in progress. Sponsor personnel who have access to treatment codes (e.g., randomization specialist, personnel directly involved with bioanalysis of serum samples, unmasked monitors performing investigational product accountability and Clinical Supplies personnel) will not divulge the codes to subjects, Investigators, site staff, and Sponsor personnel involved in the conduct of the study. Masking is maintained by providing sham injections. With this setup, subjects will continue to receive masked treatment (active or sham) monthly through the planned study duration (96 Weeks) to allow for further masked evaluation of efficacy and safety. Treatment masking will remain intact also for Investigators, and staff from the Sponsor

who have contact with subjects or Investigators or those who are involved in the direct conduct of the study until the final database lock (Week 96) has occurred.

The primary analysis at Week 48 will be performed with an unmasking of specified individuals from the Sponsor who are not involved in the direct conduct of the trial. The biostatistician who is directly involved in the conduct of the study will remain masked to treatment assignments while the study is in progress.

The document 'Process map for maintaining the mask during protocol deviation and analysis restriction determination for RTH258 in wet AMD' summarizes the procedures and actions to maintain masking to the actual treatment assignment during the pre- DBL subject evaluability assessment for the Phase III studies CRTH258A2301 and CRTH258A2302. This document was finalized prior to unmasking of these studies and is located in R&D Document Compliance Manager (RDDCM) system, Document ID: TDOC- 0053869.

Details on the conduct and logistics of the unmasked team that will perform the primary analysis are provided in the document 'Maintaining the masking of the Phase III studies (CRTH258A2301 and CRTH258A2302)' finalized prior to unmasking of these studies and located in "/CREDI Projects/R/RTH258A/CREDI Studies/RTH258A2301/Administrative Files (study level)/Validation and Planning documents - CRTH258A2302_Maintaining the Mask-20170518". This document summarizes procedures and actions implemented by Novartis to preserve the blinding of these Phase III studies after the Week 48 interim DBL and the corresponding unmasking.

1.1.3 Primary analysis

The primary safety and efficacy analysis will be based on the Week 48 data, i.e. all data up to and including Week 48. This analysis will be performed once all subjects completed their Week 48 visits or terminated the study before Week 48, while subjects continue to receive masked treatment through the planned study duration of 96 Weeks. The analysis of the data collected after the Week 48 visit will be performed once all subjects completed or discontinued from the study.

1.1.4 Data monitoring committee (DMC)

An independent Data Monitoring Committee (DMC) will be established to monitor the safety of the trial participants, and make appropriate recommendations based on the safety data reviewed.

Details on the DMC membership, responsibilities, timing of meetings, data to be reviewed, and communication with the Sponsor will be described in the DMC charter. All statistical analysis conducted for the purpose of the DMC is outside the scope of this SAP and is covered in the DMC charter and other supporting documents. The unmasked analyses for the DMC will be conducted by an independent contract research organization. Access to the unmasked analysis results will be limited to the DMC members only.

1.2 Study objectives and endpoints

1.2.1 Objectives

Primary objectives:

- To demonstrate that RTH258 is not inferior to aflibercept with respect to the change in best-corrected visual acuity (BCVA) from Baseline to Week 48

Key secondary objectives:

- To demonstrate that RTH258 is not inferior to aflibercept with respect to the change in BCVA from Baseline averaged over the period Week 36 to Week 48
- To estimate the proportion of q12 (1 injection every 12 weeks) subjects up to Week 48 in the RTH258 treatment arms
- To estimate the predictive value of the first q12 cycle for maintenance of q12 treatment up to Week 48 in the RTH258 treatment arms

Other secondary objectives:

- To evaluate the efficacy of RTH258 relative to aflibercept over the time period up to Week 96 by assessing changes in:
    - BCVA
    - Anatomical parameters of disease activity including central subfield thickness (CSFT), choroidal neovascularization (CNV) area, presence of subretinal, intraretinal, and subRPE fluid, and absence of intraretinal and subretinal fluids
    - Presence of 'q8 treatment need' including assessment of q12 status for subjects in the RTH258 3 mg and 6 mg treatment arms
    - Visual function-related patient-reported outcomes following treatment with RTH258 relative to aflibercept
- To assess the safety and tolerability of RTH258 relative to aflibercept

1.2_2 Endpoints

1.2.2.1 Efficacy Endpoints

Primary Endpoint

The primary efficacy endpoint is change in BCVA from Baseline to Week 48

Key Secondary Endpoints

The key secondary efficacy endpoints are:

- Average change in BCVA from Baseline over the period Week 36 through 48. For each subject, this endpoint is defined as the average of the changes from Baseline to Weeks 36, 40, 44, and 48.
- q12 treatment status at Week 48 (for subjects randomized to RTH258 3 mg and 6 mg only)
- q12 treatment status at Week 48 within the subjects with no q8 need during the first q12 cycle (Week 16, Week 20) (for subjects randomized to RTH258 3 mg and 6 mg only).

Additional Secondary Efficacy Endpoints

- Change in BCVA from Baseline to each postbaseline visit
- Average change in BCVA from Baseline over the period Week 84 through Week 96
- Average change in BCVA from Baseline over the period Week 4 to Week 48/96
- Average change in BCVA from Baseline over the period Week 12 to Week 48/96
- Gain in BCVA of 15/10/5 letters or more from Baseline to each postbaseline visit
- Number and percentage of subjects with BCVA of 73 letters or more at each visit
- Loss in BCVA of 15/10/5 letters or more from Baseline to each postbaseline visit
- q12 treatment status at Week 96 (for subjects randomized to RTH258 3 mg and 6 mg only)
- q12 treatment status at Week 96 within the subjects with no q8 need during the first q12 cycle (Week 16, Week 20) (for subjects randomized to RTH258 3 mg and 6 mg only)
- q8 treatment need at Week 16
- Change in CSFTtot from Baseline to each postbaseline visit
- Average change in CSFTtot from Baseline over the period Week 36 through Week 48/ over the period Week 84 through Week 96
- Average change in CSFTtot from Baseline over the period Week 4 to Week 48/96
- Change in CSFTns from Baseline to each postbaseline visit
- Average change in CSFTns from Baseline over the period Week 36 through Week 48/ Week 84 through Week 96
- Average change in CSFTns from Baseline over the period Week 12 through Week 48/96
- Change in area of CNV within the lesion from Baseline to Weeks 12, 48 and 96
- Presence of subretinal fluid (central subfield) at each postbaseline visit
- Presence of intraretinal fluid (central subfield) at each postbaseline visit
- Presence of sub RPE fluid (central subfield) at each postbaseline visit
- Simultaneous absence of subretinal and intraretinal fluid (central subfield) at each postbaseline visit
- Number of visits with simultaneous absence of subretinal and intraretinal fluid (central subfield) during Week 36 to Week 48
- Presence of subretinal hemorrhage (central subfield) at each assessment visit
- Presence of intraretinal hemorrhage (central subfield) at each assessment visit
- Simultaneous absence of subretinal and intraretinal hemorrhage (central subfield) at each assessment visit

- Change in patient-reported outcomes (VFQ-25) total and subscale scores from Baseline to Weeks 24, 48, 72 and 96

1.2.2.2 Safety Endpoints

The safety endpoints are based on the following assessments:

- Extent of exposure
- Adverse events
- General physical exam
- Vital signs
- Laboratory tests (Blood chemistry, hematology and urinalysis)
- Loss in BCVA
- Slit-lamp examination (aqueous reaction [cells and flare])
- Fundus exam (retinal hemorrhage/detachment, vitreal hemorrhage density and viu-eous cells)
- Color fundus photography (presence of geographic atrophy)
- Fundus autofluorescence (for presence and area of atrophy)
- IOP
- Post-injection assessment (gross assessment of vision, IOP, status of central retinal artery and presence of retinal detachment/new intraocular hemorrhage)

- Anti-diug antibodies (ADA) and Serum concentration ofRTH258

2 Statistical methods

2.1 Data analysis general information

The prima1y analysis at Week 48 and the final analysis after all subjects completed / te1minated the study will be performed by the Biostatistics and statistical programming groups of Nova1tis using SAS 9.4 or above.

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

Continuous variables will be summarized using the number of observations, mean, median, standard deviation, standard en ors, quartiles, minimum and maximum values. Categorical variables will be summarized with the number of observations, the number of observations for each categ01y and the co1Tes ponding frequenc y and percent. Where appropriate, two-sided 95% confidence inte1v als for point estimates of the mean or prop01tion will be provided. Point estimates and two-sided 95% confidence inte1vals of treatment group differences and p-values will be provided as appropriate.

Outputs will be presented by treatment and in addition with the overall column for the study population descriptions at baseline. Listings will include the following identifying variables: treatment, investigator number, country , subject number, age, sex, race, and visit. In addition, ocular assessments will include identification of the study and fellow eye.

2_.1 1 General definitions

lnvestigational product (IP) or ti·eatment refers to both Broclucizumab 3mg, 6mg and Aflibercept 2mg IVT injections.

Baseline (Day 1) is the date of the first study treatment in the study. The Baseline value for efficacy and safety variables is the last available value collected prior to the first treatment which can occur at the Baseline or Screening visits.

All data collected after the first study treatment are defined as *post-Baseline.* The *study day* for a post-Baseline scheduled or unscheduled visit is defined as:

Study day = (date of visit) - (date of first study ti·eatment) + 1

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

Study day = (date of visit) - (date of first study ti·eatment)

End of study/end of treat ment day mapp ing:

The *end of study* date (from the ' Visit date' fo11n in CRF) is the date when a subject completes or discontinues the study. The *"Date of Last Exposure"* (from CRF ' Exposme' form) is the date of the last study treatment on or prior to the end of study date. For rep01ting data by visit in outputs, the end of study/end of treatment visit will be allocated to the actual (rep01ted) visit number. If end of study date is not on a

scheduled visit, then end of study visit will be allocated based on study day to the closest future scheduled study visit.

Unscheduled visits:

All data collected at unscheduled visits will not be used in 'by-visit' tabulation or graphs, but they will be included for analyses based on all post-Baseline values such as LOCF imputation, safety narratives, summary of maximum decrease or increase from baseline for laboratory and vital signs data.

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

2.2 Analysis sets

Subject evaluability based on pre-specified deviations from the protocol and/or analysis requirements and their impact on analysis sets will be determined prior to locking the database for the primary analysis at Week 48 and breaking the masked treatment assignment code. Before the Week 48 database lock, the relevant protocol deviations and analysis restrictions will be specified in the deviations and evaluability plan (DEP) document with the analysis restrictions also presented in Section 5.3. The corresponding identifications at the subject level including censoring will be captured in the database and locked prior to unmasking.

2.2.1 All-Enrolled and All-Randomized Analysis Sets

All-enrolled analysis set includes all subjects who signed informed consent and are assigned subject numbers.

All-randomized analysis set (RAN) includes all subjects who were randomized in IRT.

2.2.2 Efficacy Analysis Sets

All efficacy analyses will be conducted according to the randomized treatment assignment.

2.2.2.1 Full analysis set

The full analysis set (FAS) includes all randomized subjects who receive at least one IVT injection of the study treatment. The full analysis set will serve as the primary analysis set for all efficacy analyses. The FAS represents the analysis set which is as close as possible to the intent-to-treat (ITT) principle of including all randomized subjects.

2.2.2.2 Per protocol analysis set

Supportive analyses of the primary and secondary endpoints will include analysis using the per protocol set (PPS). PPS is a subset of the FAS and will exclude subjects with protocol deviations and analysis restrictions that are expected to majorly affect the validity of the assessment of efficacy at Week 48 including for e.g. lack of compliance (including missed treatments and treatment misallocation), missing data, prohibited concomitant medication and deviation from inclusion/exclusion criteria. Discontinuation from treatment due to lack of efficacy and/or safety does not constitute a reason for exclusion from the PPS.

Before the Week 48 database lock the relevant protocol deviations and analysis restrictions as specified in the DEP will be identified at the subject level in the database. Censoring applied in relation to the specific PDs / ARs is described in Section 5.3 and the DEP.

When assessing the robustness of the overall efficacy conclusions, equal importance will be given to the FAS and PPS results understanding that a robust study will demonstrate similar conclusions from both analysis sets. Inconsistencies in key efficacy study results between the FAS and PPS will be examined and discussed in the clinical study report (CSR).

2.2.2.3 Safety Analysis Set

The safety analysis set (SAF) will include all subjectswho receive at least one IVT injection. Subjects in the safety analysis set will be analyzed according to the treatment arm from which they received majority of treatments up to and including Week 44.

To capture potential procedure related AEs occuning in subjects without having received at least one IVT injection, all AEs of randomized subjects not belonging to the SAF occuning at or after the day of randomization will be listed separately.

2.2.3 Subgroups of interest

The subgroups of interest are listed below:

- Age categoly (<75 years and ?.75 years)
- Gender (male and female)
- Baseline BCVAcategories (:S55, 56 -70, ?.71 letters)
- Baseline CSFT categoly (<400, ?.400 microns)
- Baseline lesion type (predominantly classic, minimally classic, occult)
- Baseline CNV lesion size (tertiles)
- Baseline lesion size by lesion type (predominant classic vs. minimally classic/occult) (tertiles)
- Baseline fluid status (intraretinal fluid (IRF), subretinal fluid (SRF), sub-retinal pigment epithelium (sub-RPE) fluid)
- Japanese ethnicity: Japanese vs non-Japanese
- Baseline polyps status (present/absent) from ICGA at Screening (Japanese sites only)

Subgroup analysis will be performed for the primaiy and key secondaiy efficacy variables. More details can be found in Sections 2.5.4, and 2.6.4.

2.3 Subject disposition, demographics and other baseline characteristics

Subject characteristics and study conduct summaries include tables and listings such as a subject disposition table, demographics and baseline characteristics tables, listing of treatment assignment by investigator, summaly of screen failures by reason and listing of subjects excluded from the full analysis, per-protocol and safety analysis sets including the conesponding reasons and censoring.

No tests for differences in background and demographic characteristics between treatment groups will be perfmmed. Potential related differences will be assessed based on clinical relevance.

2.3.1 Subject disposition

Subject disposition table will be based on the All-randomized analysis set. The following summaries will be included in the disposition table: number and percent of subjects who were randomized and treated (= received at least one injection), completed the study, discontinued from treatment / study overall and by reason of discontinuation. Percentages will be based on the number of subjects who are randomized. If there were dosing errors where subjects received treatment other than what they were randomized to, separate summaries will be presented based on 'as treated', while the 'as treated' status will be derived from the majority of treatments received.

A subject is considered to have completed a study period (Week 48 / Week 96) if he/she did not discontinue study prior to the end of this period. Discontinuation at Week 48 with exit visit assessment performed is considered as 'completed' for the Week 48 analysis.

Number and percent of subjects who failed screening (i.e. were not randomized) will be presented by reason using the All-enrolled analysis set. Appropriate table and listing of all screen failures along with the corresponding reason will also be presented as necessary.

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

Number and percent of subjects with major protocol deviations and analysis restrictions will be presented by deviation/restriction category. A listing of all relevant deviations will be presented.

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

2.3.2 Demographic and baseline characteristics

Demographic table will include: age (both as a continuous variable and using categories (≤64, 65 to 74, 75 to 84, and ≥85), gender, race, ethnicity. Demographic summary tables will be presented for the all-randomized, SAF, FAS and PPS.

Baseline characteristics table will include: primary diagnosis of nAMD, time since diagnosis of neovascular AMD (days), whether neovascular AMD is unilateral or bilateral, BCVA (both as a continuous variable (letters read) and using categories (≤55, 56-70, ≥71 letters read), type of CNV (predominantly classic, minimally classic, occult only), CNV location (subfoveal, juxtafoveal, extrafoveal, absent), area of CNV associated with the lesion (mm^2), presence of subretinal fluid, presence of intraretinal fluid, presence of sub RPE fluid, presence of polyps (Japan sites only), presence of retinal angiomatous proliferation (RAP), central subfield neurosensory retinal thickness (CSFTns) and central subfield thickness total (CSFTtot) (both as a continuous variable and using categories (<250, ≥250 µm) / (<400, ≥400 µm) respectively). The baseline characteristics table will be presented separately for the study and fellow eye.

A subject listing containing all demographics information by investigator will be presented using the All-randomized analysis set. The listing will also include columns for the

randomized treatment, the number of active injections by treatment and the majority of the actual treatment received for a subject.

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

2.4.1 Study treatment/ compliance

Extent of exposure to investigational product is calculated as the number of injections received. The following summaries will be presented based on the FAS and PPS.

- Overall number of treatments will be presented separately (active and sham, active only, sham only) in the following time periods:
    - Baseline to Week 8
    - Week 12 to Week 44
    - Baseline to Week 44
    - Week 48 to Week 92
    - Baseline to Week 92
- Treatment exposure by visit: The number and percent of subjects who received active, sham injections, missed a treatment (active or sham) and missed visits will be presented separately by visit and by treatment status (q8, q12) for the Brolucizumab treatment groups.
- Frequencyof all observed dosing patterns up to and including Week 44 and up to Week 92 differentiating between active and sham treatments, missed treatments and wrong treatments will be presented.
- q12/q8 allocation for RTH258 subjects by visit: Number and percent of RTH258 subjects on q12 and q8 including the number of subjects switched from q12 to q8 with related reasons.

2.4.2 Medical history, prior/concomitant medication and concomitant procedures

2.4.2.1 Medical history

Medical history (ocular and non-ocular) will be tabulated by systemorgan class and prefeITed te1m of the MedDRA dictionary using the all-randomized analysis set. Ocular events will be presented separately by study and fellow eye. A listing of all medical histmy data will be provided.

2.4.2.2 Prior medication

Prior medications (ocular and non-ocular) will be summarized using number and percentage of subjects by ATC class and prefeITed te1m according to the WHO Drug reference list dictiona1y using the all-randomized analysis set. Prior medications are those that have a start date p1 or to the first IVT injection date. Ocular medications will be presented separatdy for the study and fellow eye. Prior medications will be classified in addition as whether or not

they were ended prior to the first IVT injection date. A listing of all prior medications will be provided.

2.4.2.3 Concomitant medication

The number and percentage of subjects taking concomitant medications will be summarized by ATC class and prefen-ed term according to the WHO Drng Reference List dictionary using the safety analysis set. Medications that were taken during the trnatment period, including those that struted prior to first injection but continued after t1eatment sta1t, will be summarized as concomitant medications. Concomitant medications will be classified in addition as whether or not they sta1ted prior to first IVT injection for ocular medications, sepru·ate summaries will be presented for study and fellow eye. A listing of all concomitant medication will beprovided.

2.4.2.4 Concomitant procedures

The number and percentage of subjects who had procedures done during the study will be summarized by system organ class and prefe1Ted tenn according to the MedDRA dictionruy using the safety analysis set. For oculru·p rocedures, separate summaries will be presented for study and fellow eye. A listing of all concomitant procedures will be provided.

2.5 Analysis of the primary and first key secondary objectives

2.5.1 Primary and first key secondary endpoints

- The primary efficacy endpoint is change in BCVA from baseline to Week 48. Best-co1Tected v isual acuity will be measured based on the procedures developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) and the results will be repo1ted in letters.
- The first key seconda1y endpoint is average change in BCVA from Baseline over the period Week 36 through Week 48. For each subject, this endpoint is defined as the average of the changes from baseline to Weeks 36, 40, 44 and 48. The motivation for the choice of this endpoint is that, averaging the BCVA values over Week 36 to Week 48 will smooth out both random fluctuations and potential trough and peak values during the different treatment cycles. During the period Week 36 to Week 48, aflibercept and RTH258 subjects on q8 will have 2 assessments 4 weeks after the last dose, and 2 assessments 8 weeks after the last dose. RTH258 subjects on a q12 regimen will have 2 assessments 4 weeks after the last dose, 1 assessment 8 weeks after the last dose, and 1 assessment 12 weeks after the last dose.

The prima1y and first key seconda1y efficacy analyses will be based on the FAS with last-obse1vation-da Tied-f 01ward (LOCF) imputation of missing BCVA values.

2.5.2 Statistical hypothesis, model, and method of analysis

The statistical hypotheses for the prima1y and first key secondary endpoints are to demonstrate noninferiority of RTH258 6 mg and 3 mg to aflibercept 2 mg within a margin of 4 letters.

The following 4 hypotheses will be tested in the pre-specified hierarchical sequence according to their numbering (H_{An}, n=1, 2, 3, 4).

$_{48}$ = Week 48, $_{36\text{-}48}$ = Week 36 through 48, $_{R6(3)}$=RTH258 6(3) mg, $_{A}$=Aflibercept 2 mg

H_{01}: $\mu_{48R6} - \mu_{48A} \leqslant$ -4 letters vs	**H_{A1}**: $\mu_{48R6} - \mu_{48A} >$ -4 letters
H_{02}: $\mu_{36\text{-}48R6} - \mu_{36\text{-}48A} \leqslant$ -4 letters vs	**H_{A2}**: $\mu_{36\text{-}48R6} - \mu_{36\text{-}48A} >$ -4 letters
H_{03}: $\mu_{48R3} - \mu_{48A} \leqslant$ -4 letters vs	**H_{A3}**: $\mu_{48R3} - \mu_{48A} >$ -4 letters
H_{04}: $\mu_{36\text{-}48R3} - \mu_{36\text{-}48A} \leqslant$ -4 letters vs	**H_{A4}**: $\mu_{36\text{-}48R3} - \mu_{36\text{-}48A} >$ -4 letters

μ_{48R6}, μ_{48R3} and μ_{48A} being the corresponding unknown true mean BCVA changes from Baseline to Week 48 and $\mu_{36\text{-}48R6}$, $\mu_{36\text{-}48R3}$ and $\mu_{36\text{-}48A}$ being the corresponding unknown true mean values for the average change in BCVA from Baseline over the period Week 36 through 48.

The primary and first key secondary endpoints will be analyzed by fitting pair-wise analyses of variance (ANOVA) models with treatment, baseline BCVA categories (≤55, 56-70, ≥71 letters) and age categories (<75, ≥75 years) as fixed effects. Least square means for each treatment group and treatment differences together with corresponding two-sided 95% CIs will be derived from the fitted model. Non-inferiority is demonstrated if the lower limit of the two-sided 95% confidence interval for the corresponding treatment difference (RTH258 – aflibercept) is greater than -4 letters.

The 4 hypotheses listed above will be tested in the pre-specified hierarchical sequence according to their numbering (H_{An}, n=1, 2, 3, 4). Consequently, confirmatory testing of the second, third and fourth hypotheses requires rejection of each preceding null hypothesis. In this setting, each hypothesis will be assessed at a one-sided significance level of 0.025, while keeping the global type I error rate at 0.025.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data will be imputed using last observation carried forward (LOCF) method. Observed values from both scheduled and unscheduled visits will be used for the LOCF imputation. For subjects with no postbaseline value, the baseline value will be carried forward.

For subjects who discontinue treatment but continue in the study, the efficacy data will be censored at the time the subject started alternative anti-VEGF treatment in the study eye. No other censoring is applied within the FAS analysis of the primary and first key secondary endpoints. Censored or missing data will be imputed by the last observation prior to receiving alternative anti-VEGF treatment.

2.5.4 Supportive analyses

The following supportive analyses will be done:

1. Descriptive statistics for the primary and first key secondary endpoints will be presented based on LOCF imputation for missing /censored values using the FAS and

PPS. In addition observed data with and without censoring will be presented descriptively using the FAS. For the PPS, observed values will be presented descriptively excluding censored data. As a result within these 'observed data' – analyses for the primary endpoint, all subjects with missing Week 48 BCVA value will not be considered. Similarly, for the endpoint 'average change in BCVA from Baseline over the period Week 36 through Week 48', only non-missing values at Weeks 36, 40, 44, and 48 will be averaged for the 'observed data' analysis.

2. ANOVA using the PPS with LOCF imputation for missing/censored values. The same model as in the primary analyses will be fitted for this supportive analysis.
3. Mixed model repeated measures (MMRM) using the FAS and PPS with observed data (including censoring). The MMRM will include treatment, visit, baseline BCVA category, age category and treatment by visit interactions as fixed-effect terms and visit as a repeated measure. An unstructured covariance matrix will be used to model the within-subject error. For the MMRM analysis:
    a. The treatment difference at Week 48 will be estimated using the LSM and 95% percent confidence interval.
    b. For the endpoint of average change from Baseline over the period Week 36 through Week 48, a SAS code utilizing the ESTIMATE statement in PROC MIXED will be provided in the programming specification document to obtain the LSM estimate for the corresponding treatment difference and 95% confidence interval.
    c. If an MMRM model with unstructured covariance matrix does not converge, a more restricted covariance matrix can be considered in the following order until convergence is reached: variance components (VC), compound symmetry (CS), first-order autoregressive (AR) and Toeplitz (TOEP).
4. Subgroup analyses will be conducted to assess the consistency of treatment effect across various subgroups described in Section 2.2.3. The FAS with missing values imputed using LOCF and observed case analysis will be used for the subgroup analyses.
    a. Subgroup analyses will be conducted using the same model and analysis strategies described for the primary and first key secondary analyses 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.
    b. Subgroup analysis results will be presented using forest plots.

2.6 Analysis of the second and third key secondary objectives

2.6.1 Second and third key secondary endpoints

The second and third key secondary endpoints are:

1. q12 treatmentstatus at Week 48 (for subjects randomized to RTH258 3 mg and 6 mg only).

2. q12 treatment status at Week 48 within the subjects randomized to RTH258 3 mg and 6 mg, with no q8 need during the first q12 cycle (Week 16 and Week 20), i.e. for how many subject was a positive q12- status for the first q12 cycle predictive for the adequacy of q12 treatment up to Week 48.

2.6.2 Statistical hypothesis, model, and method of analysis

No hypothesis will be tested for the second and third key seconda1y efficacy endpoints.

The proportion of subjects with positive q12 treatment status at Week 48 in the RTH258 treatment aim s overall and within the subjects with no q8 treatment need during the first q12 cycle (Week 16 and Week 20) will be presented together with two-sided 95% confidence intervals..

While for the analysis of the overall q12 proportion, all subjects in the FAS will be considered, the analysis of the predictive value of 'no q8-need during the first q12 cycle' is based on the subset of FAS subjects with no identified q8-need at Week 16, and Week 20. For this subset a valid Week 20 diseaseactivity is required while missing the Week 16 assessment is considered as no q8-need.

During the conduct of the study, confounding effects emerged requirin g consideration to allow for a sensitive assessment of the q12 potential ofRTH258. These include the following findings:

- Early treatment / study discontinuation
- Single missed visit
- Forbidden concomitant medications/ procedures
- Discrepancy between the disease activity assessment by masked investigator and the actual treatment received (specifically over-treatment, i.e. switch to q8 treatment without identified need. Remark: related under-trnatment is not of concern as the analysis is based on the identified q8-need and not on the actual treatment).
- Other treatment allocations /applicationsdeviating from the concept of' disease activity'.

Following the estimand concept of the study protocol that consequences of lack of efficacy and/or lack of safety need adequate reflection in the efficacy estimates, the proportions of patients with a positive q12 treatment status will be derived as follows requiring duration of effect (as assessed by the q8-need) togetherwith 'sufficient efficacy and safety':

- For the 'duration of effect' requir·ement subjects will need to have the status of ' q8-need = no' at all performed disease activity assessments relevant for the coITesponding endpoint unless the status 'q8-need =yes' is confounded by reasons other than lack of efficacy and/or safety (see censming details below).
- The requiI·ement regarding 'sufficientefficacy and safety' will be addressed by considerin g subjects - even without an explicit 'q8-need=yes' - as having a negative q12 status in case any of the followmg confounding factors is attiibutable to lack of efficacy and/or lack of safety of the study treatment (assessed based on a masked medical review): 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 coITesponding q8 -need will be allocated to the next disease activity assessment visit (according to protocol) following the occmTence of such a confounding factor.

In case the missing or confounded data regarding the q12-status are attributable to reasons other than lack of efficacy and/or safety, the subject is censored within the q12-status analysis according to the following specifications (for details see 'Censoring of DAA' in the DEP and Section 5.3):

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

The estimate for the proportion of patients with a positive q12-status at Week 48 will be derived from Kaplan Meier time-to-event analyses for the event ' first q8-need' applying event allocations (in case of lack of efficacy and/or lack of safety) and censoring as described above. A corresponding 95% CI will be derived from the LOGLOG transformation (see SAS Proc Lifetest, CONFTYPE = LOGLOG).

The outcome of the Kaplan Meier analyses will be presented graphically by the estimated q12-probability over time, i.e. at each DAA-visit.

Remark: Subjects without any relevant valid disease activity assessment are considered censored at Baseline for the overall q12-proportion and at Week 20 for the analysis of the predictive value of the first q12 cycle.

2.6.3 Handling of missing values/censoring/discontinuations

The details regarding handling of missing values and discontinuations including the timing of censoring within the time-to-event analyses for the event 'first q8-need' are specified above.

2.6.4 Supportive analyses

The following supportive analyses will be performed:

1. ***' Conservative ' approach***:
   a. For the overall q12-proportion at Week 48, the denominator is the number of FAS subjects in the RTH258 3mg/ 6mg groups, and the numerator is the corresponding number of subjects with no identified q8-need at Week 16, 20, 32, and 44 (while missing the Week 20, 32 and/or Week 44 assessment leads to an allocation of q8-need as compared to a missing assessment at Week 16 which is considered as no q8- need at this visit) and no episode of overtreatment, i.e. treatments after Week 8 are limited to Week 20, 32 and 44 (and Week 56, 68, 80 and 92 for the Week 96 analysis) .

   b. Correspondingly for the q12-proportion at Week 48 in subjects with 'q8-need =no' during the first q12 cycle (Week 16 and Week 20), the denominator is the

number of FAS subjects in the RTH258 3 mg/6 mg groups with no identified q8-need at Week 16 and Week 20 (requiring a valid assessment at Week 20 while missing the Week 16 assessment is considered a no q8-need), and the numerator being the number of corresponding subjects with a positive q12 treatment status at Week 48 i.e. with additionally ' q8 need =no' at Week 32, and 44 and no episode of overtreatment (see above).

2. ***'LOCF' approach***: This approach follows in principle the same concepts as described above under the 'conservative' approach with the difference that the numerator is the number of subjects with no identified q8-need and no episode ofovertreatment, while only the available disease activity assessments are considered, i.e. missing assessments are not translated into a q8-need.

3. ***'Efficacy only' approach***: This approach follows the concept of time-to-event analysis as described above for the primary analysis approach of the q12-status with the difference only requiring 'sufficient efficacy', i.e. an allocation of a negative q12-status - even without an explicit 'q8-need=yes' - in case any of the following confounding factors is attributable to lack of efficacy of the study treatment (assessed based on a masked medical review): early treatment / study discontinuation, use of prohibited concomitant medications / procedures and/or other deviation from treatment schedule (e.g. due to a missed visit/treatment). In case of a corresponding safety reason the subject will be censored at the last valid disease activity assessment.

4. The analyses described above for the FAS will be repeated using PPS applying the same censoring and imputation concepts.
5. Subgroup analyses will be conducted to assess the consistency of the q12 proportion across various subgroups described in Section 2.2.3. These analysis will be based on the Kaplan Meier time-to-event analyses for the event ' first q8-need' as specified in section 2.6.2 using the FAS. Subgroup analysis results will be presented by the estimated q12-probability over time, i.e. at each DAA-visit and forest plots based on the 95% CI of the corresponding Week 48 probability.
6. Supportive analyses to assess the relationship between the actual investigator decisions and the treatment guidance provided in the protocol will be performed using the following analyses:
    a. For each DA assessment visit, the number and percentage of subjects who according to the treatment guidance have a q8-need (see below) will be described separately for those with and without q8 treatment-need as assessed by the investigator for all the three treatment arms. For RTH258 subjects, separately for the 3mg and 6mg arm, the same analysis will be repeated, but only up to and including the first q8 treatment need decision.

Visit	**Q8 Treatment need as derived from protocol guidance: A subject is considered to have a q8 treatment need at a given visit if at least one of the corresponding criteria is fulfilled.**

Week 16	Decrease in BCVA of ≥ 5 letters compared with Baseline Decrease in BCVA of ≥ 3 letters and CSFT increase ≥ 75 µm compared with Week 12 Presence of IRF at Week 16 while absent at Week 12 Increase in CSFTns of at least 10 microns from Week 12 to Week 16 (worsening of IRF) Decrease in BCVA of ≥ 5 letters from Week 12 AND presence of at least one of the following fluids at Week 16: IRF, SRF, and subRPE
Weeks 20, 32, and 44	Decrease in BCVA of ≥ 5 letters from Week 12 AND presence of at least one of the following fluids at the relevant visit: IRF, SRF, and subRPE
Weeks 56, 68, 80, and 92	Decrease in BCVA of ≥ 5 letters from Week 48 AND presence of at least one of the following fluids at the relevant visit: IRF, SRF, and subRPE

b. For RTH258 subjects (separately for the 3mg and 6mg arm) who were identified by the investigator as having their first q8-treatment need after Week 20, their status regarding the treatment guidance criteria at Week 16 and Week 20 will be presented. For this analysis, the number of subjects who met/did not meet the treatment guidance criteria at Week 16 and Week 20 will be presented in a cross tabulation.

c. For subjects on q12 treatment at Week 48 and who lost 5 letters or more from Week 12 to Week 48, the treatment guidance status at each of the DA assessment visits will be presented. For this analysis, the number of subjects for each of the patterns of the treatment guidance status at Weeks 16, 20, 32, and 44 will be presented in a summary table similar to the one shown below:

Week	**16**	**20**	**32**	**44**	**n (%)**
Patterns	n	n	n	n	xx (xx.x%)
	p	n	n	n	xx(xx.x%)
…	…	…	…	…	..
Total					N (100%)

Treatment guidance status: n= negative status, p=positive status

7. Comparison of new q8-treatment need during RTH258 q12 cycles and Eylea q8 cycles

a. Quantitative comparison of new q8 needs identified at 12 week-assessments for RTH58 subjects versus 4 and 8 week-assessments for Eylea

For each q12-cycle, the proportion of RTH258 subjects (relative to the subjects still on q12 and separately for the 3mg and 6mg arm) with a newly identified q8-need 12 weeks after the last injection will be compared to those Eylea subjects where a new q8 treatment need is

identified4-weeks or 8 weeks from the last injection. The following fo1mat will be used to present theresult:

RTH258 q12-cycle	RTH258 (separately for the 3mg and 6mg arm)			Eylea			
	Disease activity assessment visit	**Number of subjects at risk**	**New q8-need after 12 weeks since last treatment.**	**Disease activity assessment visit**	**Time since last treatment**	**Number of subjects at risk**	**New q8-need after 4/8 weeks since last visit.**
Week 20 - Week 32	Week 32 (last treatment Week 20)	N = number of patient 011q12 at Week 20	K1, (100*ki/ N %)	Week 32 (last treatment Week 24)	8 weeks	N=nmnber of patients 011 'q12' (=wo q8-need) at week 20	K1. (100* k;IN %)
Week 32 - Week 44	Week 44 (last treatment week 32)	N = number of patient on q12 at Week 32	K2, (100*k2,/N %)	Week 44 (last treatment week 40)	4 weeks	N =number of patients 011 'q12' (=wo q8-need) at week 40	K 2. (100*k2.IN %)
... .	... .	... .	....	....		....	....
Week 80 - Week 92	Week 92 (last treatment week 80)	N = number of patient 011q12 at Week 80	r (100* ,/N %)	Week 92 (last treatment week 84)	8 weeks	N=number of patients on ' q12' (=wo q8-need) at week 80	(100*4/N %)

Where Kir = n l.llllber of RTH258 subjects with new Q8-need after 8 weeks since last treatment on the i^{th} ql 2 cycle;

Kie = numbe r of Eylea su bject s w ith new Q8 -need afte r 4 week s sin ce last tI·eatment dtuing the ith RTH258 ql2 cycle

b. Qualitative comparison of the disease activity between treatments regarding subjects with a new q8 need identified at 12 week-assessments for RTH58 subjects versus 4 / 8 week-assessments for Eylea

For the cohorts Krr, Kie, i= 1 ,..,6 (se e a bove), the number and percentage of subjects with a positive disease activity status DA assessed according to the treatment guidance criteria given in Section 2.6.4 will be presented.

2.7 Analysis of additional secondary efficacy objective(s)

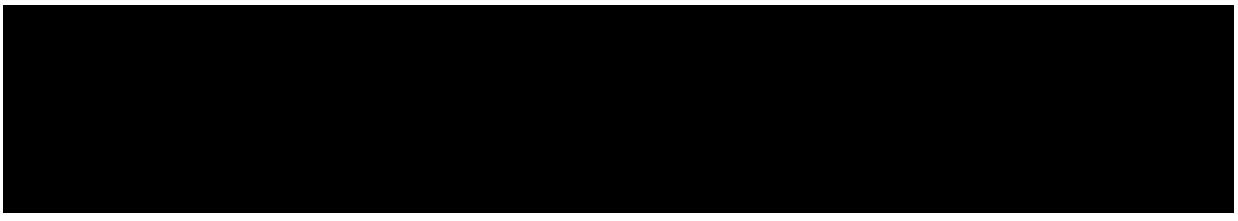
2.7.1 Se cond ary endpoint s

The seconda1y endpoints are:

- Change in BCVA from Baseline to each postbaseline visit

- Average change in BCVA from Baseline over the period Week 84 through Week 96. For each subject this endpoint is derived as the average of the changes from Baseline to Weeks 84, 88, 92 and 96
- Average change in BCVA from Baseline over the period Week 4 to Week 48. For each subject this endpoint is derived as the average of the monthly changes from Baseline up to Weeks 48
- Average change in BCVA from Baseline over the period Week 4 to Week 96. For each subject this endpoint is derived as the average of the monthly changes from Baseline up to Weeks 96
- Average change in BCVA from Baseline over the period Week 12 to Week 48. For each subject this endpoint is derived as the average of the monthly changes from Baseline to Weeks 12 up toweek 48
- Average change in BCVA from Baseline over the period Week 12 to Week 96. For each subject this endpoint is derived as the average of the monthly changes from Baseline to Weeks 12 up to Week 96
- Number and percentage of subjects with a gain in BCVA from Baseline to each postbaseline visit will be presented for the followingcriteria:
    - 2':15-letter gain
    - 2':10-letter gain
    - 2':5-letter gain
    - Note: Subjects with BCVA value of 84 letters or more at a postbaseline visit will be considered as responders for the conesponding endpoint. This is to account for a ceiling effect, e.g. for the' 2':15-letter gain' endpoint, for those subjects with BCVA values at baseline >= 70 letters.
- Number and percentage of subjects with BCVA of 73 letters or more at each postbaseline visit
- Number and percentage of subjects with a loss in BCVA from Baseline to each postbaseline visit will be presentedfor the followingcriteria:
    - 2':15-letter loss
    - 2':10-letterloss
    - 2':5-letter loss
- q12 treatment status at Week 96 (for subjects randomized to RTH258 3 mg and 6 mg only). This endpoint is analyzed using the KM method as given for the conesponding Week 48 endpoint.
- q12 treatment status at Week 96 within the subjects with no q8 need during the 1st q12 cycle (Week 16, Week 20) for subjects randomized to RTH258 3 mg and 6 mg only. This endpoint is analyzed using the KM method as given for the conesponding Week 48 endpoint.
- Number and percent of subjects with q8 treatment need at Weeks 16.

- Change in CSFT from Baseline to each postbaseline visit
- Average change in CSFT from Baseline over the period Week 36 through Week 48
- Average change in CSFT from Baseline over the period Week 84 through Week 96
- Average change in CSFT from Baseline over the period Week 4 to Week 48
- Average change in CSFT from Baseline over the period Week 4 to Week 96
- Change in CSFTns from Baseline to each postbaseline visit
- Average change in CSFTns from Baseline over the period Week 36 through Week 48
- Average change in CSFTns from Baseline over the Week 84 through Week 96
- Average change in CSFTns from Baseline over the period Week 12 through Week 48
- Average change in CSFTns from Baseline over the period Week 12 through Week 96
- Change in area of CNV within the lesion (CNV lesion size) from Baseline to Weeks 12, 48 and 96
- Number and percent of subjects with presence of subretinal fluid (central subfield) at each postbaseline visit.
- Number and percent of subjects with presence of intraretinal fluid (central subfield) at each postbaseline visit.
- Number and percent of subjects with presence of sub RPE fluid (central subfield) at each postbaseline visit.
- Number and percent of subjects with simultaneous absence of subretinal and intraretinal fluid (central subfield) at each postbaseline visit.
- Number of subjects with presence of subretinal hemonhage (central subfield) at each assessment visit
- Number of subjects with presence of intraretinal hemonhage (central subfield) at each assessment visit
- Number of subjects with simultaneous absence of subretinal and intraretinal hemonhage (central subfield) at each assessment visit
- Number of visits with simultaneous absence of subretinal and intraretinal fluid (central subfield during Week 36 to Week 48
- Change in patient-repo1ted outcomes (VFQ-25) total and subscale scores from Baseline to Weeks 24, 48, 72 and 96.



2.7.3 Statistical hypothesis, model, and method of analysis

2.7.3.1 Confirmatory testing related to additional secondary endpoints

Confirmatory hypothesis testing for additional secondary endpoints will be performed in case the proof of non-inferiority related to BCVA is successful for all 4 hypotheses specified above for the primary and key secondary endpoints.

The additional efficacy hypotheses are arranged in three sets (A-C) each linked to a different efficacy parameter containing a list of related endpoints to be tested for both RTH258 6mg and 3mg in comparison to aflibercept:

A. CSFT:
    1. Change in CSFTtot from Baseline to Week 16, 6mg
    2. Change in CSFTtot from Baseline to Week 48, 6mg
    3. Average change in CSFTtot from Baseline over the period Week 36 through Week 48, 6mg
    4. Change in CSFTtot from Baseline Week 16, 3mg
    5. Change in CSFTtot from Baseline to Week 48, 3mg
    6. Average change in CSFTtot from Baseline over the period Week 36 through Week 48, 3mg

B. Fluid-status 'yes/no' (no= absence of SRF and IRF):
   1. Fluid at Week 16, 6mg
   2. Fluid at Week 48, 6mg
   3. Number of visits without Fluid during Week 36 to Week 48, 6mg
   4. Fluid at Week 16, 3mg
   5. Fluid at Week 48, 3mg
   6. Number of visits without Fluid during Week 36 to Week 48, 3mg

C. DAA 'yes/no' (yes = q8-need according to investigators disease activity assessment):
   1. DAA at Week 16, 6mg
   2. DAA at Week 16, 3mg

All tests will be one-sided testing for superiority of RTH258 vs aflibercept, i.e.,

- for greater reductions in the CSFT change from baseline (ANOVA as specified below) with RTH258
- for a higher proportion of subjects with absence of fluid (logistic regression with treatment, age categories (<75, ≥75 years) and baseline fluid status as fixed effects) with RTH258
- for higher numbers of visits without fluid (CMH-test row mean score (scores=table) stratified by age categories (<75, ≥75 years) and baseline fluid status) with RTH258.
- for a higher proportion of subjects with 'no q8-need' (logistic regression with treatment and age categories (<75, ≥75 years) as fixed effects) with RTH258

The basis for these tests for superiority will be the FAS with last-observation-carried-forward (LOCF) imputation of missing values.

To allow for parallel testing of these three sets the global one-side alpha of 0.025 is split as follows:

- CSFT : 0.005
- Fluid (combination of SRF and IRF) : 0.01
- DAA : 0.01.

Within each set the corresponding hypotheses will be tested hierarchically according to their numbering (see above) at the local alpha-level as specified above for each set. Within this hierarchical testing approach confirmatory testing of a given hypothesis requires rejection of all preceding null hypothesis within the corresponding set and as specified above also the rejection of those related to the primary and key secondary endpoints.

Based on the graphical approach for sequential rejection of multiple test procedures (see Bretz et al , Statist. Med. 2009; 28:586–604), once all null-hypotheses related to one set could be rejected the corresponding alpha assigned to this set will be passed with a 50:50 split to the two other sets. In case also all null-hypotheses of a second set can be rejected (including

the consideration of received alpha-proportions) the hierarchical testing related to the remaining set can be done at the one-sided alpha of0.025.

fu this setting the testing of the primaly and secondary hypotheses will be controlled at the global type I enor rate of 0.025.

2.7.3.2 General analysis specification for secondary [redacted] endpoints

The analysis of secondaly efficacy endpoints will be based on the FAS with LOCF imputation for missing values. For the endpoints of q12 status at Week 96, incomplete/missing/confounded data will be handled using the same methods as specified for the KM analysis for the key secondalyendpoints ' q12 treatment status at Week 48 for subjects randomized to RTH258 3 mg and 6 mg'. Suppoltive analyses based on the PPS will be performed for endpoints related to BCVA and related to the q12 status. Additional analyses using the PPS will be conducted if the sensitivity analysis for the primalyefficacy hypothesis suggests relevant differences between FAS and PPS results. fu addition, these endpoints will also be summarized and presented descriptively.

a. Continuous endpoints:

The continuous variables will be summarized using ANOVA models similar to the one specified for the primaly endpoint. Estimates of least square means for each treatment and for the treatment differences including 95% confidence intelvals and p-values for the treatment differences will be presented. fu addition, descriptive statistics based on the obselved data only will be presented by treatment and visit.

Note:

- For CNV lesion size, lesion type will be added as a class variable and baseline lesion size categories (see conesponding subgroup categories) instead of baseline BCVA categolY
- For the ANOVA analysis of change in CSFT, baseline CSFT categolies (< 400, 2 400 Lm) will be used instead of baseline BCVA category as a class varia ble
- For the ANOVA analysis of change in nemosensory retinal thickness, the baseline nemosensoiy retinal thickness categories (<250, 2250 µm) will be used instead of BCVA category as a class variable
- Line plots (LSM ± 1 SE) will be presented for all the ' by visit ' analyses

b. Categorical variables

Propoltions and treatment differences in propolt ions along with 95% confidence intelvals and p-values will be presented using a logistic regression with the conesponding baseline status and age categories as fixed effects.

Bar chaits will be produced for all the categorical variables.

For the endpoints related to fluid / hemonhage / - status

o Shift tables comparing the status at Baseline to each/specified postbaseline visit will be presented

- For the analysis of presence of fluid by visit, additional analyses will be performed by only including subjects where the corresponding fluid was present at Baseline.
- For the analysis of the endpoint 'simultaneous absence of subretinal and intraretinal fluid', additional analysis will be performed by only including subjects where the corresponding fluids (at least one fluid type is present) were present at Baseline.
- 95% exact confidence intervals for the risk differences for the Unstratified analyses will be based on the Farrington-Manning score statistic.

2.7.4 Handling of missing values/censoring/discontinuations

Missing data will be handled using LOCF and observed case analysis (i.e. no imputation). For the endpoints of q12 status , incomplete / confounded data will be handled using the same method as specified for the KM analysis for the key secondary endpoint, q12 treatment status at Week 48.

2.8 Safety analyses

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of all the safety endpoints including, shift tables and graphical presentation.

Safety analyses described in this section will be conducted using the safety analysis set on a treatment-emergent basis. For treatment-emergent safety analyses, subjects will be analyzed according to the actual treatment they received. If a subject received both study treatments, then the subject will be analyzed based on the majority of treatments received up to and including Week 44.

In addition to capturing specific safety assessments on the corresponding eCRF pages, findings from such assessments that are deemed to be clinically significant by the investigator will also be reported as adverse events. For the safety parameters of slit lamp, fundus exam and post injection assessments (except for post-injection IOP), data captured on the corresponding eCRF pages will be presented in listings only while related clinically relevant findings will be part of the overall adverse event analysis.

Except for imputation of partial dates, no imputation will be done for missing values for all safety analyses.

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

The primary safety analyses will include all treatment-emergent data, including data collected after the subject discontinued study treatment and started alternative anti-VEGF treatment. A sensitivity analysis will be conducted in which, for subjects who discontinued treatment but continued in the study, with application of alternative anti-VEGF treatment, their safety data are censored at the time the subject started alternative anti-VEGF treatment. That is, only safety data collected prior to receiving alternative anti-VEGF treatment will be used for these analyses. These sensitivity analyses will be specified in the respective endpoint analysis.

For listings that present data from a subset of subjects who satisfy a certain criteria at one visit, data at all visits will be presented.

2.8.1 Extent of exposure

Analysis of extent of exposure is discussed in Section 2.4.1. Based on the SAP, the overall number of active and sham injections up to and including Week 48 and Week 96 will be presented descriptively (both as continuous and categorical variable). For the categorical presentation, the observed frequencies will be presented as the categories.

The number and percent of subjects who received wrong active treatment will also be presented using a shift table for 'as randomized' vs ' as treated' by visit. A listing will be provided for patients who received at least once a wrong treatment.

2.8.2 Adverse events (AEs)

The definition of Adverse Event (AE) in the study protocol is restricted to events occuning after the first treatment exposure, while for this study AEs were collected from the time of info1med consent. In this analysis plan, events that staited prior to the subject receiving treatment (= prior to day of first injection) are presented separately as pre-treatment adverse events. All AEs occuning from when a subject signs info1med consent to when a subject exits the study will be accounted for in the repo11ing. Analysis and presentation of AEs occmTing during the screening period will be separated from those occmTing during the investigational period where a comparative evaluation of treatment-emergent AEs is intended. A treatment-emergent AE is an event not present prior to exposure to investigational product or any pre-existing event that worsens following exposure to investigational product. The period for treatment-emergent AE analysis sta1ts from the first exposure (= first injection) to the investigational product until the subject exits the study.

Summa1ies (counts and percentages) for specific AEs will be presented by system organ class (SOC) and prefened te1m (PT) according to the Med.DRA dictiona1y. Ocu lar and non-ocular (systemic) AEs will be presented separately. Oculai· AEs will be presented by study and fellow eye separately. In addition to an overall presentation of AEs, rep01ts will be generated for special classes of AEs such as serious AEs (SAE), AEs resulting in treatment and/or study discontinuation, most frequent AEs (2 % in any treatment group for each PT), investigational product/administration procedure-related AEs, AEs by maximum severity, AEs of special interest and AEs of potential relevance to intravitreal anti-VEGF class.

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

A sensitivity analysis excluding AEs that sta1ted after a subject discontinued study treatment and sta1ted alternative anti-VEGF treatment will be presented for the overall AE and SAE tables. Additionall y, for subjects who discontinue treatment and sta1ted alternative anti-VEGF treatment, a separate table (oculai·, and non-oculai-) by SOC and PT for AEs with onset date after sta1tof alternative anti-VEGF treatment will be presented. Additionally, for subjects who received different active treatments, a separate table by system organ class and PT for AEs with onset date after the subject received the non-randomized active treatment will be presented.

For subjects who were randomized but did not receive an injection, a subject listing will be provided that includes all AEs that occun ed at or after the day of randomization until the subject discontinued/exited from the study using the All-randomized analysis set.

A subject listing will be provided for AEs that occur after signing inform ed con se nt but pri o r to ex p os ure to investigational product using the All-emolled analysis set. These listings will comprise all events occun ing during this period in any subject who consented to palt icipate in the study.

The SOCs will be presented in alphabetical order. Prefen ed terms will be ordered within each SOC by decreasing incidence in the Brolucizumab 6 mg treatment arm. The MedDRA version used for report ing the study will be the latest available prior to the database lock and will be described in a footnote.

Summary tables for in-text prese ntations will be summarized by PT.

2.8.2.1 Adverse events of special interest (AESIs)

The AESis specified in the protocol are the following:

- Endophthalmitis
- Grade 3 aqueous flare/Grade 4 aqueous cells (see MOP for grading scale)
- Grade 2 aqueous flare/Grade 3 aqueous cells that fails to decrease to 1 or less within 30 days of the onset of the event (see MOP for grading scale)
- 30 letter decrease in BCVA compared with Baseline visual acuity
- Sustained (> 15 minutes) loss of light perception due to elevated IOP
- IOP > 30 mmHg at/past 60 minutes post-injection
- Any elevation ofI OP requiring surgical intervention(e.g., paracentesis)
- New retinal tear or detachment
- New vitreous hemon hage > 2+ severity that does not resolve within 14 days of the onset of the event (seeMOP for grading scale)
- New diagnosis of geographicatrophy

AESis will be identified by the investigator on the AE eCRF page and will be summarized using counts and percentages by system organ class and prefen ed term accor ding to the MedDRA dictionary. A subject listing will also be presented for AESis.

A sensitivity analysis excluding AESis that start ed after a subject discontinued study treatment and started alternative anti-VEGF treatment will be presented for the AESI table. Additionally, for subjects who discontinue treatment, a separate table for AESis with onset date after start of alternative anti-VEGF treatment will also be presented.

2.8.2.2 AEs of potential relevance tointravitreal anti-VEGFclass

Tables and Listings for AEs with potential relevance to the intravitreal anti-VEGF class will also be presented, and summarized (counts and percentages) by system organ class and prefenedterm according to the MedDRAdictionary. Ocular and non-ocular (systemic) AEs

will be presented separately. Ocular AEs will be presented by study and fellow eye separately. These AEs are presented in the table (Table 1) below.

Table 1 AEs of potential relevance to intravitreal anti-VEGF class

Safety Topic Of Interest	SOC	Data Domain	MedDRA Code	MedDRA Term	MedDRA Level	MedDRA Qualifier	Location*
Venous thromboembolic events	Vascular disorders	MEDDRA	90000105	Venous thromboembolic events (excl. ocular) [LUCENTIS] (CMQ)	NMQ1		NO
Arterial Thromboembolic Events	Vascular disorders	MEDDRA	20000061	Central nervous system haemorrhages and cerebrovascular conditions (SMQ)	MQ2	NARROW	NO, SE, FE
Arterial Thromboembolic Events	Vascular disorders	MEDDRA	20000043	Ischaemic heart disease (SMQ)	MQ1	NARROW	NO
Arterial Thromboembolic Events	Vascular disorders	MEDDRA	20000082	Embolic and thrombotic events, arterial (SMQ)	MQ2		NO, SE, FE
Infectious Endophthalmitis	Infections and infestations	MEDDRA	90000101	Infectious endophthalmitis [LUCENTIS] (CMQ)	NMQ1	NARROW	SE, FE
Intraocular pressure increase	Investigations	MEDDRA	90001788	Increased intraocular pressure [RETINA] (CMQ)	NMQ1		SE, FE
Traumatic Cataract	Eye disorders	MEDDRA	90001787	Traumatic cataract [RETINA] (CMQ)	NMQ1		SE, FE
Retinal arterial occlusive events	Eye disorders	MEDDRA	90004735	Retinal artery occlusive events [RTH258] (CMQ)	NMQ1		SE, FE
Systemic Hypersensitivity	Immune system disorders	MEDDRA	20000214	Hypersensitivity (SMQ)	MQ1	NARROW	NO
Non-ocular haemorrhage	Vascular disorders	MEDDRA	90000106	Non-ocular haemorrhages [LUCENTIS] (CMQ)	NMQ1		NO
Systemic hypertension	Vascular disorders	MEDDRA	20000147	Hypertension (SMQ)	MQ1	NARROW	NO

Safety Topic Of Interest	SOC	Data Domain	MedDRA Code	MedDRA Term	MedDRA Level	MedDRA Qualifier	Location*
Glaucoma	Eye disorders	MEDDRA	90001789	Glaucoma without IOP [RETINA] (CMQ)	NMQ1		SE, FE
Vitreous haemorrhage	Eye disorders	MEDDRA	10047655	Vitreous haemorrhage	PT		SE, FE
Retinal pigment epithelial tear	Eye disorders	MEDDRA	10062971	Retinal pigment epithelial tear	PT		SE, FE
Retinal detachment and retinal tear	Eye disorders	MEDDRA	90001746	Retinal detachment and retinal tear [STANDARD] (NMQ)	NMQ1	NARROW	SE, FE
Intraocular inflammation**	Eye disorders	MEDDRA	90004793	Intraocular inflammation [RTH258] (CMQ)	NMQ1		SE, FE

NO = non-ocular; SE = study eye; FE = fellow eye Intraocular inflammation AEs will be evaluated in pre-specified sub-categories (Endophthalmitis, Anterior Uveitis, Posterior Uveitis, and Other). Preferred terms for these intraocular inflammation sub-categories are presented in Table 9.*

2.8.3 Deaths

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

2.8.4 Laboratory data

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

Hematology (Complete Blood Count)

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

Observed values and change from baseline values for each hematology parameter will be presented descriptively by visit and treatment group. In addition, descriptive summaries will be presented graphically using boxplots. For the parameters presented in Table 2, each value will be categorized as low, normal or high using the clinically notable ranges as given in the table. A shift table showing category of each parameter at baseline relative to each post-baseline visit, to the last assessment, to the most extreme increase and most extreme decrease will be presented by treatment group.

The number and percent of subjects satisfying the liver event / liver laboratory trigger criteria shown in Table 3 will also be presented by visit.

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

Blood Chemistry

The following blood chemistry parameters will be collected: blood urea nitrogen (BUN), serum creatinine, BUN/creatinine ratio, uric acid, cholesterol, triglycerides, albumin, total globulin, A/G ratio, total serum iron, total protein, serum electrolytes (sodium, potassium, bicarbonate, chloride, calcium, magnesium), phosphorus, glucose and the following liver function tests (LFT): serum aspartate transaminase [AST (SGOT)], serum alanine transaminase [ALT (SPGT)], alkaline phosphatase, gamma glutamyl transaminase (GGT), total bilirubin, direct bilirubin, indirect bilirubin and lactate dehydrogenase (LDH).

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

Urinalysis

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

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

Table 2 Clinically notable laboratory values

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

Table 3 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	3 x ULN < ALT/AST ≤ 5 x ULN 1.5 x ULN <TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST >5 × ULN
	ALP >2 × ULN (in the absence of known bone pathology)
	TBL >2 × ULN (in the absence of known Gilbert syndrome)
	Potential Hy's Law cases (defined as ALT or AST >3 × ULN and TBL >2 × ULN [mainly conjugated fraction] without notable increase in ALP to >2× ULN)
	Any clinical event of jaundice (or equivalent term)*
	ALT or AST >3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia**
	Any adverse event potentially indicative of a liver toxicity***

* AE based on clinical judgement and the lab parameter of total bilirubin (TBL).

** The Lab time of ALT/AST detection has to be within the start and end date of any of the AEs. The PTs for these events are: Malaise, Fatigue, Abdominal pain, Nausea, Vomiting, Drug reaction with eosinophilia and systemic symptoms, Eosinophilic cellulitis, Allergic eosinophilia.

*** These events cover the following (broad clinical terms for hepatic illnesses): hepatic failure, fibrosis and cirrhosis, and other liver damage related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms

TBL: total bilirubin; ULN: upper limit of normal

2.8.5 Other safety data

2.8.5.1 Loss in BCVA

Counts and percentages of subjects with a predefined decrease in BCVA from Baseline to each post-baseline visits, to the last assessment and maximum loss from Baseline to any post-baseline assessment visit will be presented for the following cut off points: ≥10-letter loss, ≥15-letter loss ≥30-letter loss.

A listing of all subjects with a ≥15-letter loss in BCVA from baseline to any post-baseline visit will be presented. For subjects who had ≥15-letter loss at any visit, BCVA values at all visits will be presented.

2.8.5.2 Intraocular pressure

Intraocular pressure (IOP) measurements will be recorded in mmHg and rounded to the nearest whole number.

Descriptive summaries of pre-injection observed values and change from baseline IOP values will be presented at each study visit by treatment. Line plots of the mean change in IOP values

with error bars representing ± standard error by visit and treatment will be presented. The x-axis will be study visit and the y-axis will be the change from Baseline value.

A summary table with counts and percentages of subjects with observed IOP of >30 mmHg will be presented separately for pre- and post-injection by visit. In addition, counts and percentages of subjects with IOP >30 mmHg at the last assessment and at any postbaseline visit will be presented.

A summary table with counts and percentages of subjects with observed pre-IOP ≥21 mmHg in 3 consecutive scheduled visits will also be presented.

A subject listing of all IOP measurements will be pressed by visit. In addition, a listing of all subjects with observed IOP of more than 30 mmHg at any visit will be presented. For subjects with observed IOP >30 mmHg at any visit, IOP values at all visits will be presented.

2.8.5.3 Vital signs

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

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

Table 4 Clinically notable changes in 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

A line plot of mean change from baseline in the vital sign parameter by study visit and treatment with error bars representing ±1 standard error will be presented. The x-axis will be study visit and the y-axis will be the mean change from baseline value.

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

2.8.5.4 Slit Lamp examination

A slit-lamp examination will be performed to evaluate the anterior segment of the eye, including lid/lashes, conjunctiva, cornea, lens, iris, aqueous cells and aqueous flare. All data collected on the corresponding eCRF page will be presented in a subject listing.

2.8.5.5 Fundus examination

Fundus examination will be performed to evaluate the health of the retina, macula, choroid, optic nerve, and vitreous. The retina will also be assessed for retinal detachment/tear and hemorrhage and the vitreous will be evaluated for hemorrhage and vitreal cells. All data collected on the fundus exam eCRF page will be presented in a subject listing.

2.8.6 Presence of geographic atrophy

Shift tables comparing Baseline vs post baseline values for presence of geographic atrophy (central subfield) from color fundus photography, as graded by the central reading center, will be presented. In addition, shift tables comparing the Baseline value to the last assessment visit, and to any visit with a presence of geographic atrophy will also be presented. Geographic atrophy will also be assessed based on presence (shift tables) and area of atrophy (descriptive statistics) on fundus autofluorescence within the subset of sites which provided these data.

2.8.7 Post-injection assessment

Post-injection parameters to be evaluated in the study eye are gross assessment of vision, the status of the central retinal artery, presence of retinal detachment, new intraocular hemorrhage(s) and IOP.

A summary table with counts and percentage of subjects with IOP increase of ≥10, ≥20 mmHg from pre-injection to post-injection will be presented by visit, at the last visit, and at any visit. IOP assessment done at 30 (±15) minutes post-injection will be used for this analysis. Separate summaries will be presented for active and sham injections.

The difference in the pre-and post-injection IOP values will be presented descriptively by treatment and visit. Separate summaries will be presented for active and sham injections.

A listing for subjects with post-injection IOP increase of ≥10 mmHg from pre-injection IOP will also be presented.

All other post-injection assessment data collected on the eCRF will be presented in subject listings.

2.8.8 Presence of anti-drug antibody (ADA)

Blood samples to test for serum anti-drug antibody (ADA) will be collected following pre-determined sample collection time points. Number and percent of subjects according to their ADA status (ADA negative, ADA positive without boost, induced, boosted) will be presented by treatment and by intraocular inflammation AE status (Table 9). In addition, ADA titer pattern and shift table showing ADA titer at baseline relative to each post-baseline assessment visit, relative to the last assessment visit, and to any visit with most extreme increase in ADA titer will be presented by treatment. Subject listing of all ADA titer values will be presented for all subjects and separately for subjects with an intraocular inflammation AE.

Patient profile plots (including both efficacy and safety endpoints) will be presented for subjects with ADA status ‘induced’ and/or ‘boosted’. The visits where a positive ADA result is confirmed will be shown on the subject profile plot.

ADA data up to Week 36 will be analyzed for the Week 48 primary analysis. The final Week 96 analysis will include all ADA data.

2.9 Pharmacokinetic endpoints

A subject listing will be provided for all subjects that have detectable RTH258 sernm concentration value at any of the PK assessment visits.

For each assessment time-point, the mean RTH258 serum concentration will be provided together with the percentage of subjects with a detectable con esponding concentration level. For the assessment visits after Week 12 theses presentations will be categorized by the time since last injection of RTH258 (categories: 4/8/12 weeks).

2.10 Subject-reported outcome

2.10.1 Visual function questionnaire (VFQ-25)

Each subscale score has a range of 0 to 100 inclusive and will be calculated from the re-scaled raw data as described in Table 5. A missing response will not be re-scaled (except for the response to question 15c, see below, which will be re-set to 0 if the response to question15b is1).

The answers to questions will be re-scaled as follows to calculate the total and subscale scores.

Table 5 Rescaling of VFQ-25 questions

Answer to question	Rescaling for questions 1, 3, 4 and 15c	Rescaling for question 2	Rescaling for questions 5 - 14, 16 and 16a	Rescaling for - questions 17 - 25
1	100	100	100	0
2	75	80	75	25
3	50	60	50	50
4	25	40	25	75
5	0	20	0	100
6	NA	0	NA	*NIA*

- Note that the answer to question 15c will subsequently be adjusted based on the answer to question 15b.
  - If the answer to 15b is 1 then the answer to 15c will be re-set to 0.
  - If the answer to 15b is 2 or 3 then the answer to 15c will be re-set to missing

The general health rating is the re-scaled answer to question1.

Response choice "6" indicates that the person does not perform the activity because of non-vision related problems. If this choice is selected, the item is coded as "missing". Subscales will be calculated where at least one of the (re-scaled) questions contributing to that subscale is non-missing, and otherw ise se t to missing. The scales and co1Tesp o ndin g questions are shown in Table 6.

Table 6 Questions contributing to VFQ subscales

Subscale	Questions
General vision	2
Ocular pain	4 and 19
Near activities	5, 6 and 7
Distance activities	8, 9 and 14
Social functioning	11 and 13
Mental health	3, 21, 22 and 25
Role difficulties	17 and 18
Dependency	20, 23 and 24
Driving	15c, 16 and 16a
Color vision	12
Peripheral vision	10

The composite score is the average of the 11 subscales shown in Table 6. It will be set to missing if at least six of the subscales are missing.

Descriptive summary statistics for rescaled values and change from baseline to post baseline VFQ assessment visits will be presented using the full analysis set for the composite and subscale scores. Mean changes from baseline to each post baseline VFQ assessments visits will be compared between the study treatment groups and the control group. Appropriate statistical methods (CMH or ANCOVA Model with treatment and the corresponding baseline value in the model) will be used for treatment group comparisons. Additionally, descriptive statistics will also be presented for the general health score. All analysis will be done on the rescaled values. The change from baseline will derived based the changes in the individual items scores and then averaged for the subscale score.

The VFQ-25 composite score and subscale scores will also be presented in a subject listing.

2.11 Interim analysis

No interim analysis prior to the primary analysis at Week 48 is planned for this study.

3 Sample size calculation

A sample size of 297 subjects per treatment arm is sufficient to demonstrate noninferiority (margin = 4 letters) of RTH258 3 mg/6 mg versus aflibercept 2 mg with respect to the BCVA change from Baseline to Week 48 at a two-sided alpha level of 0.05 with a power of approximately 90% assuming equal efficacy and a common standard deviation of 15 letters. A power of at least 90% can be expected for the first key secondary endpoint assuming that averaging over the 4 time points will not lead to an increase in the standard deviation.

To account for a drop-out rate of 10%, a total of 330 subjects will be randomized per treatment arm (990 total).

4 Change to protocol specified analyses

TI1e following additional seconda1y endpoints that were not specified in the protocol were added to this statistical analysis plan.

- [redacted]
- [redacted]
- [redacted]
- Number and percentage of subjects with BCVA of 73 letters or more at each postbaseline visit
- [redacted]
- Average change in CSFTtot from Baseline over the period Week 4 to Week 48/96
- Average change in CSFTtot from Baseline over the period Week 12 through Week 48/96
- Average change in CSFTtot from Baseline over the period Week 36 through Week 48/ over the period Week 84 through Week 96
- Average change in CSFTns from Baseline over the period Week 36 through Week 48/ Week 84 through Week 96
- Average change in CSFTns from Baseline over the pe1iod Week 12 through Week 48/96
- Presence or absence of subretinal and intraretinal (central subfield) hemonhage
- Number of visits with simultaneous absence of subretinal and intraretinal fluid (central subfield during Week 36 to Week 48
- [redacted]

The followingsubgroups of interest were added:

- Baseline fluid status (IRF, SRF, sub-RPE)
- CNV lesion size

Following additional safety endpoint that were not specified in the protocol were added to this statistical analysis plan

- Presence of geographic atrophy from color fundus photography

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

5.1.1.1 Adverse event end date imputation

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

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

5.1.1.2 Adverse event start date imputation

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

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

The following matrix explains the logic behind the imputation.

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

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

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

2. Else AE start reference date = treatment start date

Impute AE start date -

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 imputation

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

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

Concomitant treatments with partial start dates will have the date or dates imputed. The following table explains the notation used in the logic matrix

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

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) 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 Statistical models

5.2.1 Primary and first key secondary analysis

The ANOVA, MMRM and logistic regression models, will be fitted using data from two treatments at a time. That is, separate models will be fitted for RTH258 3mg vs Aflibercept 2mg, and RTH258 6mg vs Aflibercept 2mg.

Analysis of Variance (ANOVA)

The following ANOVA model will be used for the primaiy and first key secondary efficacy endpoints:

<change from Baseline in BCVA at Week 48> <average change from Baseline in BCVA from Week 36 to Week 48> = intercept + treatment + Baseline BCVA category + age category + error.

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

```
PROC MIXED DATA=<Dataset> order=Internal;
        CLASS <Treatment> <BCVA CAT> <AGE CAT> ;
        MODEL <Chg_VA> = <Treatment> <BCVA CAT> <AGE CAT>/ SOLUTION
        LSMEANS Treatment> / DIFF CL ALPHA = 0.05 OM;
        ODS OUTPUT LSMEANS=outLsm DIFFS=Diffs;
RUN;
```

Where

<Chg_VA> = primary/first key secondary efficacy endpoint

<BCVA CAT> = baseline BCVA category

<AGE CAT> = age category

<Treatment>= randomized treatment assignment

The terms in the brackets are to be adjusted according to the real data set and variable names. For the above analysis, the data structure is one record per FAS subject. Data will include all subjects in the FAS.

Mixed Model Repeated Measures (MMRM)

The following MMRM model will be used for the supportive analysis of the primary and first key secondary efficacy variables:

<change from Baseline in BCVA at Week 48> <average change from Baseline in BCVA from Week 36 to Week 48> = intercept + treatment + Baseline BCVA category + age category + visit + treatment*visit + error.

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

```
PROC MIXED DATA=<Dataset> order=Internal;
        CLASS USUBJID <Treatment> <VISIT> <BCVA CAT> <AGE CAT>;
        MODEL <Chg_VA> = <Treatment> <VISIT> <BCVA CAT> <AGE CAT>
      <VISIT>*<Treatment>
                / solution DDFM=KENWARDROGER ALPHA=0.05;
        REPEATED <VISIT>/type=UN subject=USUBJID;
        LSMEANS <VISIT>*<Treatment> / DIFF CL ALPHA = 0.05 om;
        ODS OUTPUT LSMEANS=outLsm DIFFS=Diffs;
RUN;
```

where

<Chg_VA> = primary/first key secondary efficacy endpoint

<BCVA CAT> = baseline BCVA category

<AGE CAT> = age category

<Treatment> = randomized treatment assignment

…<VISIT> = ordered visit number

Note:

For the above MMRM analysis, the data structure is one record per FAS 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. Instead, the value will be passed to the model as missing.

5.2.2 Key secondary analysis

The following pseudo SAS code will be used for the logistic regression analysis

```
PROC LOGISTIC DATA= data;
        CLASS <Treatment> (REF = "C" ) <BCVA CAT> <AGE CAT> /PARAM=REF;
        MODEL <RESP> (EVENT = '1') = <Treatment> <AGE CAT> <BCVA CAT>
                /ALPHA = 0.05;
        ODS OUTPUT PARAMETERESTIMATES=parameters;
        ODS OUTPUT ODDSRATIOS= OR;
RUN;
```

where,

<RESP> = binomial endpoint.

<BCVA CAT>= baseline BCVA category

<AGE CAT> = age category

<Treatment> = randomized treatment assignment

Note:

- For the above analyses, the data structure is one record per subject and visit.
- The least square mean estimates obtained from the above model are for the log-odds ratios. The estimated difference in proportions and the corresponding 95% confidence intervals will be obtained by applying the delta method. The pseudo SAS code to derive the treatment difference and 95% CI from the least square mean output of the fitted model will be provided in the programming specification document.

5.3 Subject evaluability and censoring

Protocol deviations (PD) and analysis restrictions (AR) considered to be critical for subject evaluability regarding the prima1y and key seconda1y endpoints are described in the Deviations and Evaluability Plan (DEP) document.

The definition of PDs is provided in the DEP and follows the concept of major/impo1tant protocol deviations as outlined in the Guideline (ICH) E3.

AR's address limitations in the evaluability which result from missing or confounded data with underlying background not qualifying as a PD (e.g. early study terminations, early treatment discontinuations, missing visits / missed treatments)

Subject evaluability is based on two components:

- Exclusion from an analysis set
- Censoling of specific data points from an 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)
- Lack of safety / tolerability of the study treatment (=2)
- Other (=O)

R e m ar k: B ase d o n the con cept o f PD ' s, th e ir underl ying reason will always be ' O'.

As a ge nera l rnle ARs with a reason of 1 or 2 do not lead to an exclusion from any anal ysis set, as a potential link between exclusion reason and treatment would constitute a source for a systematic bias.

Table 7 specifies the general criteria leading to exclusion from one or more analysis sets.

Table 7 Subject Classification

Analysis Set	Criteria that cause subjects to be excluded
RAN	Not randomized
FAS	Not in the RAN Did not receive at least one study in jec ti o n
PP S	Not in the FAS No valid BCVA assessment during the period Week 36 to Week 48 with an underlying reason = 0.
SAF	Did not receive at least one study injection

Table 8 summarizes the concepts of censoring for the prima1y parameters BCVAand ql 2-status/DAA applied to the two efficacy analysis sets FAS and PPS. The details for the timing of censoring for BCVAand DAA are specified in the DEP Table 8-1 in relation to PDs and in Table 8-2 in relation to ARs.

Table 8 Censoring concepts for BCVA and DAA within their primary analysis approaches

Analysis Set	Efficacy parameter	Censoring concept
FAS	BCVA	No censoring related to PDs or ARs. Remark: See section 2.5.3 and 2.5.4 for censoring / handling of BCVA data afier switch to alternative anti-VEGF treatment.
FAS	DAA	The censoring specified in the DEP Tables 8-1 and 8-2 is applied the same way for FAS and PPS, with the option for additional specification in form of (FAS:n) in case of PDs / ARs leading to exclusion from PPS. Remark: The primary analysis of the q12 propo1tion as derived from DAA and described in section 2.6.2 applies censoring in case the underlying DAA is considered to be confounded by reasons other than 1 or 2. Based on the underlying time-to-' first-q8-need' anlysis all info1mation up to and including the censoring time-point contribute to the evaluation of the q12 status.
PPS	BCVA	The censoring specified in the DEP Tables 8-1 and 8-2 for BCVA is applied Remark: Censoring related to switch to standard of care is applied in the same was as for the FAS
PPS	DAA	The censoring specified in the DEP Tables 8-1 and 8-2 for DAA is applied

In case a subject has multiple PDs/ARs with impact on his/her evaluability the following rnles are applied:

- A subjectis excluded from an analysis set if at least one PD or AR with this consequence was identified. This rnle is built on the concept of the medical assessment of the 'reason' which considers the reason of an earlier event to potentially also be the reason for following PDs or ARs.
- In case of multiple censoring time points censoring will be perfom1ed at the earliest.

- For a single case an adjustmentsof censoring was applied to account for an equalization between two PDs/ARs. For details see footnote to DEP Tables 8-1 / 8-2 / censoring code '6'.

Table 9 Preferred Terms for Intraocular Inflammation

List of PTs: Other	List of PTs: Anterior Uveitis	List of PTs: Posterior Uveitis	List of PTs: Endophthalmitis
Optic neuritis	Anterior chamber cell	Vitritis	Pseudoendophthalmitis
Cogan's syndrome	Anterior chamber fibrin	Ocular vasculitis	Non-infectious endophthalmitis
Idiopathic orbital inflammation	Ciliary hyperaemia	Vitreous haze	Endophthalmitis
Toxic anterior segment syndrome	Aqueous fibrin	Retinitis	Panophthalmitis
Uveitis-glaucoma-hyphaema syndrome	Anterior chamber flare	Retinal vasculitis	
Acute zonal occult outer retinopathy	Anterior chamber inflammation	Noninfective retinitis	
Macular oedema	Iritis	Noninfective chorioretinitis	
Oculomucocutaneous syndrome	Iridocyclitis	Chorioretinitis	
Periorbital oedema	Cyclitis	Choroiditis	
Ocular sarcoidosis	Cholesterolosis bulbi	Uveitis	
Birdshot chorioretinopathy			
Cyclitic membrane			
Tubulointerstitial nephritis and uveitis syndrome			
Ophthalmia neonatorum			

List of PTs: Other	List of PTs: Anterior Uveitis	List of PTs: Posterior Uveitis	List of PTs: Endophthalmitis
Vogt-Koyanagi-Harada syndrome			
Ocular pemphigoid			
Eye inflammation			
Ocular hyperaemia			
Retinal oedema			
Oculorespiratory syndrome			
Autoimmune uveitis			
Chorioretinopathy			

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06/12/2017 21:17:43	[redacted]	Biostats
06/12/2017 21:53:53	[redacted]	Management of Affected Area Approval