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Short Title

Efficacy and Safety of RTH258 versus Aflibercept

Long Title

A Two-Year, Randomized, Double-Masked, Multicenter, Two-Arm Study Comparing the Efficacy and Safety of RTH258 6 mg Versus Aflibercept in Subjects with Neovascular Age-Related Macular Degeneration

Protocol Number:	RTH258-C002 / NCT02434328
Study Phase:	3
Sponsor Name and Address:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099
Investigational Product:	RTH258 solution for intravitreal injection, 6 mg / 50 µL
US IND# / EudraCT	IND# 112023 / 2014-004886-26
Indication Studied:	Neovascular Age-Related Macular Degeneration
Investigator Agreement:	I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practices (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements. Additionally, I will comply with all procedures for data recording and reporting, will permit monitoring, auditing, and inspection of my research center, and will retain all records until notified by the Sponsor.

Principal Investigator:

Signature Date

Name:

Address:

1 SYNOPSIS

Sponsor:	Alcon Research, Ltd. 6201 South Freeway Fort Worth, Texas 76134-2099	**Protocol Number:** RTH258-C002
Investigational Product:	RTH258, formerly ESBA1008	**Study Phase:** ☐ 1 ☐ 2 ☒ 3 ☐ 4 ☐ N/A
Active Ingredient:	RTH258 6mg	
Protocol Title:	A Two-Year, Randomized, Double-Masked, Multicenter, Two-Arm Study Comparing the Efficacy and Safety of RTH258 6 mg versus Aflibercept in Subjects with Neovascular Age-Related Macular Degeneration	
Investigator(s)/ No. of Sites:	Multicenter; approximately 200 sites	
No. of Subjects	Approximately 660 randomized	
Duration of Treatment:	96 weeks	
Study Population:	Subjects ≥ 50 years of age with untreated active choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) in the study eye	

Objective(s):

Primary:

- To demonstrate that RTH258 6 mg is not inferior to aflibercept 2 mg with respect to the change in best-corrected visual acuity (BCVA) from Baseline to Week 48

Secondary:

- To demonstrate that RTH258 6 mg is not inferior to aflibercept 2 mg 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 6 mg treatment arm
- To estimate the predictive value of the first q12 cycle for maintenance of q12 treatment up to Week 48 in the RTH258 6 mg treatment arm
- To evaluate the efficacy of RTH258 6 mg relative to

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aflibercept 2 mg over the time period up to Week 96 by assessing changes in:

- BCVA
- Anatomical parameters of disease activity including central subfield thickness (CSFT) and CNV area
- Presence of "q8 treatment need", including assessment of q12 status for patients in the RTH258 6 mg treatment arm

- To assess visual function-related, subject reported, outcomes following treatment with RTH258 6 mg relative to aflibercept 2 mg
- To assess the safety and tolerability of RTH258 6 mg relative to aflibercept 2 mg

Methodology:

This study has 2 arms with 1:1 randomization. Subjects in both arms will have visits every 4 weeks through Week 96. The primary analysis will be performed at Week 48.

In Arm 1 (RTH258 6 mg):
RTH258 6 mg will be initially injected 3 times at 4 week intervals, at Visit 1/Baseline, Visit2/Week 4 and Visit 3/Week 8.

Following these 3 loading doses, each subject will be injected every 12 weeks (q12) up to Visit 24/Week 92 unless there is disease activity assessed according to the guidance provided at Visit 5/Week 16, Visit 6/Week 20, Visit 8/Week 28, Visit 9/Week 32, Visit 11/Week 40, Visit 12/Week 44, Visit 14/Week 52, Visit 15/Week 56, Visit 17/Week 64, Visit 18/Week 68, Visit20/Week 76, Visit 21/Week 80 or Visit 23/Week 88. If disease activity is identified, the subject will be reassigned to receive injections every 8 weeks (q8) thereafter, up to study exit. The interactive response technology (IRT) system will make the necessary changes to the dosing per the masked Investigator's assessment. The disease activity assessment will also be performed at visit 24/Week 92 but will not be entered into IRT and will have no

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effect on the subject's treatment regimen.

Disease activity Criteria at 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
- Decrease in BCVA of ≥ 5 letters **due to neovascular AMD disease activity** compared with Week 12
- New or worse intraretinal cysts (IRC)/ intraretinal fluid (IRF) compared with Week 12

Disease Activity Criterion at Weeks 20, 28, 32, 40 and 44:

- Decrease in BCVA of ≥ 5 letters due to neovascular AMD disease activity compared with Week 12

Disease Activity Criterion at Weeks 52, 56, 64, 68, 76, 80, 88 and 92:

- Decrease in BCVA of ≥ 5 letters due to neovascular AMD disease activity compared with Week 48

In Arm 2 (aflibercept 2 mg):
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 q8 up to Visit 24/Week 92.

Treatments:

Investigational Product: RTH258 6 mg / 50 µL
Route of Administration: IVT injection
Duration of Treatment: 96 Weeks

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	Dosage:	6 mg RTH258 in 50 µL (120 mg/mL formulation)
	Control Article:	Aflibercept 2 mg / 50 µL
	Route of Administration:	IVT injection
	Duration of Treatment:	96 Weeks
	Dosage:	2 mg of aflibercept in 50 µL

Subject Selection:

Inclusion Criteria:

1. Subjects must give written informed consent before any study level related procedures are performed
2. Subjects must be 50 years of age or older at Screening
3. Active CNV lesions secondary to AMD that affect the central subfield (including retinal angiomatous proliferation [RAP] lesions with a CNV component) in the study eye at Screening and confirmed by the Central Reading Center (CRC)
4. Total area of CNV (including both classic and occult components) must comprise > 50% of the total lesion area in the study eye at Screening and confirmed by the CRC
5. Intra and/or subretinal fluid affecting the central subfield of the study eye at Screening and confirmed by the CRC
6. BCVA between 78 and 23 letters, inclusive, in the study eye at Screening and Baseline using Early Treatment Diabetic Retinopathy Study (ETDRS) testing

Exclusion Criteria:

1. Any active intraocular or periocular infection or active intraocular inflammation (e.g., infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis) in either eye at Baseline
2. Central subfield of the study eye affected by fibrosis or geographic atrophy assessed by color fundus photography at Screening and confirmed by the CRC
3. Total area of fibrosis ≥ 50% of the total lesion in the study eye at Screening and confirmed by the CRC
4. Subretinal blood affecting the foveal center point and/or ≥ 50% of the lesion of the study eye at Screening and confirmed by the CRC
5. Subject has received any approved or investigational treatment for neovascular AMD (other than vitamin supplements) in the study eye at any time

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6. Any history or evidence of a concurrent intraocular condition in the study eye, including retinal diseases other than neovascular AMD, that, in the judgment of the Investigator, could require medical or surgical intervention during the course of the study to prevent or treat visual loss that might result from that condition, or that limits the potential to gain visual acuity upon treatment with the investigational product.
7. Retinal pigment epithelium (RPE) rip/tear in the study eye at Screening
8. Current vitreous hemorrhage or history of vitreous hemorrhage in the study eye within 4 weeks prior to Baseline
9. History or evidence of the following in the study eye:
    - intraocular or refractive surgery within the 90 day period prior to Baseline
    - previous penetrating keratoplasty or vitrectomy
    - previous panretinal photocoagulation
    - previous submacular surgery, other surgical intervention or laser treatment for AMD
10. Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication or according to Investigator's judgment at Screening
11. Aphakia and/or absence of the posterior capsule in the study eye at Screening
12. Intra- or periocular use of corticosteroids in the study eye during the 6 month period prior to Baseline
13. Use of topical ocular corticosteroids in the study eye for 60 or more consecutive days within the 90 day period prior to Baseline
14. Use of systemic corticosteroids for 30 or more consecutive days within the 90 days prior to Baseline, with the exception of low stable doses of corticosteroids (defined as ≤ 10 mg prednisolone or equivalent dose used for 90 days or more prior to Baseline). Inhaled, nasal or dermal steroids are permitted
15. Previous therapeutic radiation near the region of the study eye
16. Treatment with aflibercept (EYLEA®), bevacizumab (AVASTIN®) or pegaptanib (MACUGEN®) within the 4 week period prior to Baseline, or with Ranibizumab, 0.5 mg (LUCENTIS®) within the 2 week period prior to

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Baseline in the nonstudy eye

17. History of a medical condition (disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding) that, in the judgment of the Investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product
18. History of hypersensitivity to any component of the test article, control article, or clinically relevant sensitivity to fluorescein dye, as assessed by the Investigator
19. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG pregnancy test.
20. Women of child-bearing potential, defined as all women less than 1 year postmenopausal or less than 6 weeks since sterilization (further definition can be found in Section 12.7) at Baseline, unless they are using highly effective methods of contraception during dosing of study treatment. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before Baseline. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to Baseline). For female subjects in the study, the vasectomized male partner should be the sole partner for that subject
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception
    - Placement of an intrauterine device (IUD) or

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intrauterine system (IUS)

21. Participation in an investigational drug, biologic, or device study within 30 days or the duration of 5 half-lives of the investigational product (whichever is longer) prior to Baseline *Note: observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary*
22. Systemic anti-vascular endothelial growth factor (VEGF) therapy within the 90 day period prior to Baseline
23. Stroke or myocardial infarction in the 6 month period prior to Baseline
24. Uncontrolled blood pressure defined as a systolic value ≥ 160 mmHg or diastolic value ≥ 100 mmHg at Screening

In cases where both eyes are eligible, the eye with the worse BCVA at Baseline will be selected as the study eye. If both eyes have the same BCVA, it is recommended to select the right eye as the study eye.

Assessments:

Efficacy:

- BCVA using ETDRS methodology
- Spectral domain optical coherence tomography (SD-OCT)
- Fluorescein angiography (FA)
- National Eye Institute Visual Function Questionnaire-25 (VFQ-25)

Safety:

- General physical exam
- Vital signs
- Blood chemistry/hematology/urinalysis
- Anti-drug antibody (ADA) assessments
- Systemic RTH258 assessment
- Complete ophthalmic exam:
  - Slit-lamp exam
  - IOP measurement (pre/postinjection)
  - Fundus exam (dilation at the discretion of the Investigator)
- Postinjection assessments
- Treatment emergent adverse events including events of special interest (ESIs; Section 12.3)

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Other:

- Color fundus photography
- Fundus autofluorescence (at a subset of sites)

Statistical Methods:

Primary Efficacy Endpoint:

- Change in BCVA from Baseline to Week 48

Key Secondary Efficacy Endpoint:

- 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.
- q12 treatment status at Week 48 (for subjects randomized to RTH258 6 mg only)
- q12 treatment status at Week 48 with no q8 need during the 1st q12 cycle (at Week 16, Week 20) (for subjects randomized to RTH258 6 mg only)

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
- 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 6 mg only)
- 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 6 mg only)
- Change in CSFT from Baseline to each postbaseline visit
- Change in neurosensory retinal thickness from Baseline to each postbaseline visit
- Change in CNV lesion size from Baseline to Weeks 12, 48 and 96

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- Absence of subretinal fluid at each postbaseline visit
- Absence of intraretinal fluid at each postbaseline visit
- q8 treatment need at Weeks 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88 and 92
- Change in patient reported outcomes (VFQ-25) total and subscale scores from Baseline to Weeks 24, 48, 72 and 96

Safety Endpoints:

- Incidence and characteristics of treatment emergent adverse events
- Treatment emergent changes in ocular and systemic parameters
- Change in ADAs from Baseline to Weeks 12, 24, 36, 48, 68 and 88
- Extent of systemic RTH258 at Weeks 12, 24, 36, 48, 68 and 88

Statistical Methods:

Confirmatory testing for efficacy:

Hypotheses: The following non-inferiority hypotheses are related to a non-inferiority margin of 4 letters.

$_{48}$ = Week 48, 36-48 = Week 36 through 48, $_{R6}$=RTH258 6mg, $_{A}$=aflibercept 2 mg

$\mathbf{H_{01}}$: $\mu_{48R6} - \mu_{48A} \leq -4$ letters vs $\mathbf{H_{A1}}$: $\mu 4_{8R6} - \mu 48_{A} > -4$ letters

μ_{48R6} and μ_{48A} being the corresponding unknown true mean BCVA changes from Baseline to Week 48.

$\mathbf{H_{02}}$: $\mu_{36\text{-}48R6} - \mu_{36\text{-}48A} \leq -4$ letters vs $\mathbf{H_{A2}}$: $\mu_{36\text{-}48R6} - \mu_{36\text{-}48A} > -4$ letters

$\mu_{36\text{-}48R6}$ 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.

Primary analysis data set:

The primary efficacy analysis data set is the full analysis set (FAS) with missing values imputed by last observation carried forward (LOCF). The FAS includes all subjects who are

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randomized and received at least one IVT injection. Sensitivity analyses will be performed using the per protocol analysis set (PPS) and alternative imputation for missing values including a mixed model repeated measures (MMRM) and observed data only analyses.

Statistical testing strategy:

The 2 hypotheses will be tested in the pre-specified hierarchical sequence according to their numbering (HAn, n=1,2). Consequently, confirmatory testing of the second hypothesis requires rejection of the first null hypothesis. In this setting, each hypothesis will be assessed at a two-sided $\alpha = 0.05$, while keeping the global type I error rate at 0.05.

Statistical method:

Two-sided 95% confidence intervals (CI) for the differences in means, RTH258 6 mg – aflibercept 2 mg, based on analysis of variance (ANOVA) model with treatment, Baseline BCVA categories (≤ 55, 56-70, ≥71 letters), and age categories (< 75, ≥ 75 years) as fixed effects will be presented for the primary efficacy analysis. The same ANOVA model will be fitted for the key secondary endpoint, average change in BCVA from Baseline over the period Week 36 through 48.

Within the specified hierarchical testing strategy, noninferiority will be established if the lower limit of the corresponding 95% CI is greater than -4 letters (corresponding to the noninferiority margin of 4 letters).

Sample size:

A sample size of 297 subjects per treatment arm is sufficient to demonstrate noninferiority (margin = 4 letters) of RTH258 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

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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.

1.1 Amendments

Amendment 3

Purpose of amendment:

The primary purpose of this amendment is to allow ADA analysis of the samples collected from aflibercept treated patients (Section 10.7.5). Minor clarifications have also been made to Sections 9.4, 10.1, 10.7.4, 10.9 and 12.3

Amendment 2

Purpose of amendment:

The primary purpose of this amendment is to incorporate changes which resulted from interactions with Regulatory Authorities. In addition changes have been made to clarify some inclusion/exclusion criteria and study procedures.

Rationale:

Revision 1: (*Section 1 Synopsis, Section 2 Overview of Study Plan, Section 10.2.1 Screening Visit (Day -14 to Day -2) and Section 10.2.2 Visit 1 Baseline (Day 0)* Requirement of BCVA in the study eye to be between 78 and 23 letters, inclusive, at Screening as well as Baseline.

Rationale: The purpose of this change is to further clarify the intention of the protocol that the criterion must be met at both the Screening and Baseline Visit by stating it explicitly.

Revision 2: (*Section 10.7.6 Analysis of Pharmacogenetics*) the statement that instruction regarding the Pharmacogenetic samples can be found in the MOP has been removed.

Rationale: This was a typo in the original protocol, instructions for the samples can be found in the Central Laboratory Manual.

Revision 3: (Section 2. Overview of Study Plan and Section 10.7.16 Postinjection Assessment): Simplification of the postinjection assessment.

Rationale: This change is to make post injection fundoscopy at the discretion of the investigator, thereby reducing the risk of postinjection IOP rise due to pupil dilatation.

Revision 4: (*Section 10.8 Concomitant Treatment and Section 10.9 Prohibited Treatment*) Allowance of all treatments in the nonstudy eye which are approved for exudative AMD in the respective country.

Rationale: This change has been made to ensure subjects have unrestricted access to approved treatment in the nonstudy eye.

Revision 5: (*Section 11.9 Safety)* Section 11.9.4 Safety parameters several bullet points were added and Section 11.9.5 Adverse Events, Section 11.10 Interim Analyses and Section 11.11 Sample Size Justification were added.

Rationale: Inadvertently between the original protocol and version 2 of the protocol these bullet points and sections had been removed. This is to correct this and place them back into the protocol.

Current study status:

Case Report Form Revision Required:	☐ Yes	☒ No
Informed Consent Modification Required:	☒ Yes	☐ No
Applicable Investigators:	☐ Yes	☐ Selected (list below)

Itemized Changes:

Notable changes to the protocol are listed in the summary below using strike through for deletions and underlined font for insertions Notable changes to the protocol are listed in the summary below using strike through for deletions and underlined font for insertions.

Section 1 SYNOPSIS

Inclusion criteria:

6. BCVA between 78 and 23 letters, inclusive, in the study eye at Screening and Baseline using Early Treatment Diabetic Retinopathy Study (ETDRS) testing

In cases where both eyes are eligible, the eye with the worse BCVA at Baseline will be selected as the study eye. If both eyes have the same BCVA, it is recommended to select the right eye as the study eye.

Section 2 OVERVIEW OF STUDY PLAN

Subscript:

7. ~~If~~ BCVA ~~cannot~~ must be performed at the Screening ~~Visit, the BCVA may be only performed~~ and at the Baseline Visit to qualify the subject.
13. Whether the subject receives an active injection or sham injection, the study eye will be evaluated 0-5 minutes and 30 (±15) minutes postinjection to ensure that the injection procedure and/or the investigational product have not endangered the health of the eye. This includes an evaluation of central retinal artery perfusion via ~~includes~~ gross assessment of vision~~, status of central retinal artery, presence of retinal detachment, presence of new intraocular hemorrhage(s),~~ and measurement of IOP. Direct visualization to assess the central retinal artery, presence of retinal detachment, presence of new intraocular hemorrhage(s) might be appropriate at the discretion of the investigator and/or based on the results of gross assessment of vision and IOP measurement.

Section 10.2.1 Screening Visit (Day -14 to Day -2)

7 Perform BCVA on both eyes. ~~If BCVA cannot be performed at the Screening visit, the BCVA may be performed at the baseline visit to qualify the subject.~~

Section 10.2.2 Visit 1/Baseline (Day 0)

~~Subject eligibility will be determined at Screening. However, if the BCVA is not able to be assessed at the Screening Visit, the Baseline BCVA may be used to qualify the subject. Baseline BCVA of the study eye must be between 78 and 23 letters, inclusive, for the subject to qualify.~~

14. Have the unmasked Investigator perform an IVT injection according to the randomization/kit assignment. The injection procedure may be performed at a later time, as long as it is within 7 days of the scheduled visit ~~and within the visit window~~.

Section 10.7.6 Analysis of Pharmacogenetics

Details on the collections and shipment of the samples are provided to Investigators in the laboratory manual ~~and MOP~~.

Section 10.7.16 Postinjection Assessment

The study eye will be assessed before, immediately (0-5 minutes) after and 30 (± 15) minutes after each IVT/sham injection to ensure that the procedure and/or the study medication have not endangered the health of the eye. The postinjection assessments include an evaluation of central retinal artery perfusion via a gross assessment of vision (eg, count fingers)~~, the status of the central retinal artery, presence of retinal detachment, presence of new intraocular hemorrhage(s)~~ and measurement of IOP according to the schedule detailed in the MOP. Direct visualization to assess the central retinal artery, presence of retinal detachment, presence of new intraocular hemorrhage(s) might be appropriate at the discretion of the investigator and/or based on the results of gross assessment of vision and IOP measurement.

Section 10.8. Concomitant Treatment

The Investigator should instruct the subject to notify the study site about any new medications he/she takes after enrolling into the study.

Should the nonstudy eye require treatment during the study with an anti-VEGF, ~~ranibizumab~~ a drug which is approved for the treatment of exudative AMD in the respective country should be applied at the discretion of the Investigator and following the procedures established at the respective site. The nonstudy eye treatment may occur at any time once the Baseline study eye injection has been administered.

Table 10.9.-1: Prohibited Treatment

Nonstudy eye: Unapproved or Investigational treatment ~~Anti-VEGF therapy other than ranibizumab~~

Section 11.9.4 Safety parameters

The following safety parameters will be descriptively analyzed to assess treatment emergent changes or changes specifically related to the injection procedure using postinjection assessments:

- Adverse events
- General physical exam
- Vital signs
- Laboratory tests (blood chemistry, hematology and urinalysis)

- Worsening in BCVA
- Slit-lamp examination
- Fundus exam
- IOP
- Postinjection assessment
- ADA levels
- Systemic RTH258 levels

Section 11.9.5 Adverse Events

AEs will be coded using the MedDRA dictionary and presented by system organ class and preferred term. Treatment emergent AEs will be analyzed based on the number and percentage of subjects with at least one AE in the category of interest. Separate presentations will be provided related to ocular events in the study eye and nonstudy eye and non-ocular events. Additional summaries will be provided by severity and causality (separately assessed for the injection procedure and the drug). Serious Adverse Events and adverse events leading to discontinuation of study treatment will also be summarized separately.

Subject listings of all adverse events will be provided. Deaths and other serious or clinically significant non-fatal adverse events will be listed separately.

Events of special interest (ESIs; as defined in section 12.3) will be presented based on their incidences.

Section 11.10 Interim Analyses

The primary efficacy analysis will be based on the Week 48 data. The database, including all Week 48 data, will be locked once all active subjects have completed the Week 48 Visit. Systemic RTH258 and ADA data up to Week 36 will be analyzed for the Week 48 primary analysis. The primary analysis at Week 48 will be performed with an unmasking of specified Novartis/Alcon individuals who are not involved in the direct conduct of the trial.

Subjects will remain in the study and will continue to receive masked treatment through the planned duration (96 Weeks) to allow for further masked evaluation of efficacy and safety. Treatment masking of individual subjects will remain intact for all subjects, Investigators, and Alcon staff who have contact with subjects or Investigators or those who are involved in the direct conduct of the study until the final database lock has occurred.

Section 11.11 Sample Size Justification

A sample size of 297 subjects per treatment arm is sufficient to demonstrate noninferiority (margin = 4 letters) of RTH258 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.

Amendment 1

Purpose of amendment:

The primary purpose of this amendment is to implement required changes received from regulatory authorities and address aspects of the study that would avoid unnecessary exclusions of patients who would be appropriate for the study inclusion.

Rationale:

Revision 1: (*Section 1 Synopsis, Section 2 Overview of Study Plan, Section 5.1.2 Treatment Regimen Rationale, Section 10.1 Outline of Study, Figure 10.1-1 Dosing Schedule by Treatment, Section 10.2.4 Visit 4/Week 12 through Visit 24/Week 92, Section 10.7.13 Disease Activity Assessment and Section 11.5.2 Statistical Methods)* Disease Activity Assessments have been added for Visit 8/Week 28, Visit 11/Week 40, Visit 14/Week 52, Visit 17/Week 64, Visit 20/Week 76, Visit 23/Week 88.

Rationale: Regulatory Authority request to include Disease Activity Assessments at these time points.

Revision 2: (*Section 1. Synopsis*) Exclusion criteria no. 4 central subfield has been changed to foveal center point.

Rationale: The current wording unnecessarily excludes patients who are appropriate for anti-VEGF treatment. The change would reduce unnecessary screen failures and improve recruitment.

Revision 3: (*Section 1. Synopsis, Section 12.7 Pregnancy in the Study*) Exclusion criteria no. 20 refers to section 12.7 for further definitions of women of childbearing potential and post-menopausal. Additionally the of use of highly effective birth control for use during the study and for a period of up to 3 months post final study injection as per EYLEA label has been added to section 12.7.

Rationale: Request from Regulatory Authorities to add highly effective wording and provide expanded definition of WOBC and menopausal and add the 3 months use of study mandated birth control after last study injection as per comparator label.

Revision 4: (*Section 1. Synopsis*) Exclusion criteria no. 23 has changed the period prior to Baseline for stroke and myocardial infarction from 90 days to 6 month period.

Rationale: Request from Regulatory Authorities to extend this period.

Revision 5: (*Section 5.1.2. Treatment Regimen Rationale*) providing justification of the choice of a 2-arm trial in relation to a 3-arm trial with a placebo arm included in the study protocol.

Rationale: Request from Regulatory Authorities to provide this justification.

Revision 6: (*Section 5.1 Study Rationale and Background*) Addition of a sub-section 5.1.3. Non-inferiority margin rationale.

Rationale: Regulatory Authority request to justify the chosen non-inferiority margin.

Revision 7: (*Section 7 Amendments*) Clarification on sponsor responsibility gain approval from Regulatory Authorities for amendments prior to implementation.

Rationale: Regulatory Authority request to clarify this approval in the protocol.

Revision 8: (*Section 9 Treatment Administration*) Additional information to clarify the randomization process.

Rationale: Regulatory Authority request for more information relating to the process of randomization, the explanation should be extended about the procedure how the sequence assignment is generated.

Revision 9: (*Section 10.5 Discontinuation of Study Treatment and Section 10.6 Clinical Study Termination*) Details more instances where there should be consideration to discontinue

study treatment for a patient and provides additional guidance or instances when a clinical study would be terminated.

Rationale: Regulatory Authority request to provide more rules on the discontinuation of study treatment and clinical study termination.

Revision 10: (*Section 10.7.4 Laboratory Analysis of Blood and Urine*) Information regarding the details around the samples to be collected for blood and urine that can be found in the MOP.

Rationale: Clarification based on a request from the Regulatory Authority regarding specificity of samples to be collected for the study.

Revision 11: (*Section 11.5. Primary and Key Secondary Efficacy Analyses*) addition of text to describe that analysis of the primary and first key secondary endpoints will also be performed based on the per protocol set.

Rationale: Analysis would allow for the direct comparison of full analysis set results and per protocol set results within the assessment of the robustness of the efficacy conclusion. To further strengthen the importance of the per protocol set for the overall efficacy conclusions the additional text has been provided as per request for an update to the analysis plan by the Regulatory Authorities.

Revision 12: (*Section 11.6 Additional Secondary Efficacy Analyses*) Aligning with the synopsis as intended analysis.

Rationale: Change in synopsis not carried through to section 11 during review, correction.

Revision 13: (*Section 12.3 Procedures for Recording and Reporting AEs and SAEs*) SAE reporting requirements have been updated in the protocol according to GCP guidelines.

Rationale: Regulatory Authority instruction that Sponsor is required to amend the Protocol and clarify the Sponsor's reporting responsibility in the protocol.

Revision 14: (*Section 13 Data Handling and Administrative Requirements)* Section 13.5 Data Monitoring Committee added

Rationale: Regulatory Authority instruction that Sponsor is required to implement DMC.

Current study status:

Case Report Form Revision Required:	☐ Yes	☒ No
Informed Consent Modification Required:	☒ Yes	☐ No
Applicable Investigators:	☐ Yes	☐ Selected (list below)

Itemized Changes:

Notable changes to the protocol are listed in the summary below using strike through for deletions and underlined font for insertions Notable changes to the protocol are listed in the summary below using strike through for deletions and underlined font for insertions.

Section 1 Synopsis

Methodology:

In Arm 1 (RTH258 6 mg):
RTH258 6 mg will be initially injected 3 times at 4 week intervals, at Visit 1/Baseline, Visit2/Week 4 and Visit 3/Week 8.

Following these 3 loading doses, each subject will be injected every 12 weeks (q12) up to Visit 24/Week 92 unless there is disease activity assessed according to the guidance provided at Visit 5/Week 16, Visit 6/Week 20, Visit 8/Week 28, Visit 9/Week 32, Visit 11/Week 40, Visit 12/Week 44, Visit 14/Week 52, Visit 15/Week 56, Visit 17/Week 64, Visit 18/Week 68, Visit 20/Week 76, ~~or~~ Visit 21/Week 80 or Visit 23/Week 88. If disease activity is identified, the subject will be reassigned to receive injections every 8 weeks (q8) thereafter, up to study exit. The interactive response technology (IRT) system will make the necessary changes to the dosing per the masked Investigator's assessment. The disease activity assessment will also be performed at visit 24/Week 92 but will not be entered into IRT and will have no effect on the subject's treatment regimen.

Disease activity Criteria at 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
- Decrease in BCVA of ≥ 5 letters **due to neovascular AMD disease activity** compared with Week 12
- New or worse intraretinal cysts (IRC)/ intraretinal fluid (IRF) compared with Week 12

Disease Activity Criterion at Weeks 20, 28, 32, 40 and 44:

- Decrease in BCVA of ≥ 5 letters **due to neovascular AMD disease activity** compared with Week 12

Disease Activity Criterion at Weeks 52, 56, 64, 68, 76, 80, 88 and 92:

- Decrease in BCVA of ≥ 5 letters **due to neovascular AMD disease activity** compared with Week 48

Exclusion criteria:

4. Subretinal blood affecting the ~~central subfield~~ foveal center point and/or ≥ 50% of the lesion of the study eye at Screening and confirmed by the CRC
20. Women of child-bearing potential, defined as all women less than 1 year postmenopausal or less than 6 weeks since sterilization (further definition can be found in Section 12.7) at Baseline, unless they are using highly effective methods of contraception during dosing of study treatment. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before Baseline. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to Baseline). For female subjects in the study, the vasectomized male partner should be the sole partner for that subject
    - ~~Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository~~
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
23. Stroke or myocardial infarction in the ~~90 day~~ 6 month period prior to Baseline

	Screening	Visit 1/ Baseline	Visit 2/ Week 4	Visit 3/ Week 8	Visit 4/ Week 12	Visit 5/ Week 16	Visit 6/ Week 20	Visit 7/ Week 24	Visit 8/ Week 28	Visit 9/ Week 32	Visit 10/ Week 36	Visit 11/ Week 40	Visit 12/ Week 44	Visit 13/ Week 48
	Day -14 to -2	Day 0	Day 28 ± 3 Days	Day 56 ± 3 Days	Day 84 ± 7 Days	Day 112 ± 7 Days	Day 140 ± 7 Days	Day 168 ± 7 Days	Day 196 ± 7 Days	Day 224 ± 7 Days	Day 252 ± 7 Days	Day 280 ± 7 Days	Day 308 ± 7 Days	Day 336 ± 7 Days
Disease Activity Assessment						X	X		X	X		X	X	

	Visit 14/ Week 52	Visit 15/ Week 56	Visit 16/ Week 60	Visit 17/ Week 64	Visit 18/ Week 68	Visit 19/ Week 72	Visit 20/ Week 76	Visit 21/ Week 80	Visit 22/ Week 84	Visit 23/ Week 88	Visit 24/ Week 92	Visit 25/ Week 96 Exit[1][4]
	Day 364 ± 7 Days	Day 392 ± 7 Days	Day 420 ± 7 Days	Day 448 ± 7 Days	Day 476 ± 7 Days	Day 504 ± 7 Days	Day 532 ± 7 Days	Day 560 ± 7 Days	Day 588 ± 7 Days	Day 616 ± 7 Days	Day 644 ± 7 Days	Day 672 ± 7 Days
Disease Activity Assessment	X	X		X	X		X	X		X	X	

Section 5 Introduction

Section 5.1 Study Rationale and Background

The primary statistical analysis compared RTH258 4.5 mg and 6.0 mg versus ranibizumab 0.5 mg with both doses achieving noninferiority. Notable however was the median time to receiving standard of care which was 45.0 days for ranibizumab but was longer for the RTH258 3.0 mg, 4.5 mg and 6.0 mg doses (75.0 days (p=0.0374), 60.0 days (p=0.1805) and 75.0 days (p=0.0360) respectively). The interquartile range was 30 – 75 days for ranibizumab, and 45 – 120 days, 30 – 120 days and 37.5 – 150 days for the RTH258 3.0 mg,

4.5 mg and 6.0 mg respectively. ~~in the 6.0 mg group compared with 45 days in the ranibizumab group), suggesting a longer duration of treatment effect.~~ RTH258 6 mg was the highest dose tested in the study and no unexpected safety issues were reported that would preclude further clinical development.

Section 5.1.2 Treatment Regimen Rationale

In the current study, RTH258 patients will receive q12 maintenance dosing. Disease activity assessments will be conducted by a masked investigator at Weeks 16, 20, 28, 32, 40 and 44, allowing ~~4~~ 6 time points up to the primary endpoint of the study (Week 48) where RTH258 q12 subjects can be reassigned to q8 treatment. It is expected that early determination at Week 16 and Week 20 of subjects who are more suited to a q8 dosing regimen will minimize the percentage of q12 subjects who will require reassignment at later time points.

Due to the well-established efficacy of anti-VEGF treatments in the indication of neovascular Age-Related Macular Degeneration, an internal validation of this study via a placebo arm is ethically not feasible. The available historical evidence of the efficacy of Lucentis (Anchor and Marina) and of aflibercept (VIEW 1 and 2) allows for a reliable estimate of the drug's effect size compared to placebo and due to the similarity of the current NI trial to the historical studies in terms of study population, efficacy assessments and duration, there is a sound basis for external validation of the results of this study.

Section 5.1.3 Non-inferiority Margin Rationale

5.1.3 Non-inferiority Margin Rationale

Non-inferiority testing related to the primary efficacy parameter best corrected visual acuity [letters] will be based on a margin of 4 letters. This non-inferiority margin provides assurance that both absolute efficacy and acceptable efficacy relative to the active comparator aflibercept can be established.

- Absolute efficacy: The active comparator aflibercept together with Lucentis belongs to a class of anti-VEGF treatments where for the individual products similar efficacy has been established (VIEW 1 and 2). This similarity justifies the use of the only

available related superiority data versus Sham or Visudyne reported for monthly Lucentis in the studies MARINA (vs Sham) and ANCHOR (vs Visudyne) to quantify the order of magnitude of the absolute treatment effect for this class of treatments. For the endpoint 'change in BCVA from baseline to Month 12 [letters]' this absolute treatment effect was estimated for monthly Lucentis 0.5mg in the MARINA study as 17.5 letters (95%CI [14.8 , 20,2]) compared to Sham-injections and in the ANCHOR study as 21.1 letters (95% CI [17.5 , 24.6]) compared to Visudyne . Relative to these absolute treatment effects, non-inferiority established at a 4 letter margin will guarantee an absolute treatment effect in the magnitude of at least 10 letters even under the conservative approach of using the lower limits of these 95% confidence intervals as reference.

- Establishing acceptable efficacy relative to the active comparator aflibercept: For a non-inferiority margin of 4 letters together with the assumed standard deviation of 15 letter for the primary endpoint BCVA change from baseline at Week 48 and a sample size of 300 patients, it is expected that non-inferiority can only be claimed if the observed difference between RTH258 and aflibercept is > -1.6 letters. Signifying that the observed mean BCVA change for RTH258 is no more than 1.6 letters worse than for aflibercept.

  The power calculation is based on the assumption of equal efficacy for RTH258 and aflibercept with a resulting power of about 80% for two successful Phase III studies, while in case of a real treatment difference of -1.6 letters the power goes down to 25%. Even if the treatment difference is only -1 letter, the chance for two successful Phase III studies falls below 50%.

  While a 4 letter difference in the BCVA response between two regimens can be considered of relevance, a 4 letter non-inferiority margin in a clinical trial leads to a discrimination of treatments already for much smaller delta-levels for which minor underlying clinical relevance can be attributed.

Section 7 Amendments

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments will be created by the Sponsor and must be approved by the IEC/IRB and Regulatory Authorities prior to implementation except when required to

mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Section 9 Treatment Administration

Section 9.4 Subject Confidentiality and Methods Used to Minimize Bias

Treatment will be assigned to subjects through the IRT system. Each subject number will be associated with treatment groups according to a random process generated using computer software (SAS 9.2 PROC PLAN). Subjects will be assigned ~~treatment in numerical order~~ in sequence number order according to time of randomization; the randomization schedule will be blocked to ensure a balance of treatment allocations across the study. There are no stratification factors in this study. The IRT system will be utilized to implement the outcome of the disease activity assessments at the appropriate visits.

Section 10 Study Procedures

Section 10.1 Outline of Study

In Arm 1 (RTH258 6 mg):

RTH258 6 mg will be initially injected 3 times at 4 week intervals, at Visit 1/Day 0, Visit 2/Week 4 and Visit 3/Week 8.

Following the loading doses, each subject will be injected q12 up to Visit24/Week 92 unless there is disease activity assessed according to the guidance provided at Visit 5/Week 16, Visit 6/Week 20, Visit 8/Week 28, Visit 9/Week 32, Visit 11/Week 40, Visit 12/Week 44, Visit 14/Week 52, Visit 15/Week 56, Visit 17/Week 64, Visit 18/Week 68, Visit 20/Week 76, ~~or~~ Visit 21/Week 80 or Visit 23/Week 88. If disease activity is identified, the subject will be reassigned to receive injections q8 thereafter, up to study exit. The IRT system will make the necessary changes to the dosing per the masked Investigator's assessment. The disease activity assessment will also be performed at visit 24/Week 92 but will not be entered into IRT and will have no effect on the subject's treatment regimen.

Disease Activity Criteria at Week 16:

- Decrease in BCVA of ≥ 5 letters compared with Baseline

- Decrease in BCVA of ≥ 3 letters and CSFT increase ≥ 75µm compared with Week 12
- Decrease in BCVA of ≥ 5 letters due to neovascular AMD disease activity compared with Week 12
- New or worse IRC/IRF compared with Week 12

Disease Activity Criterion at Weeks 20, 28, 32, 40 and 44:

- Decrease in BCVA of ≥ 5 letters due to neovascular AMD disease activity compared with Week 12

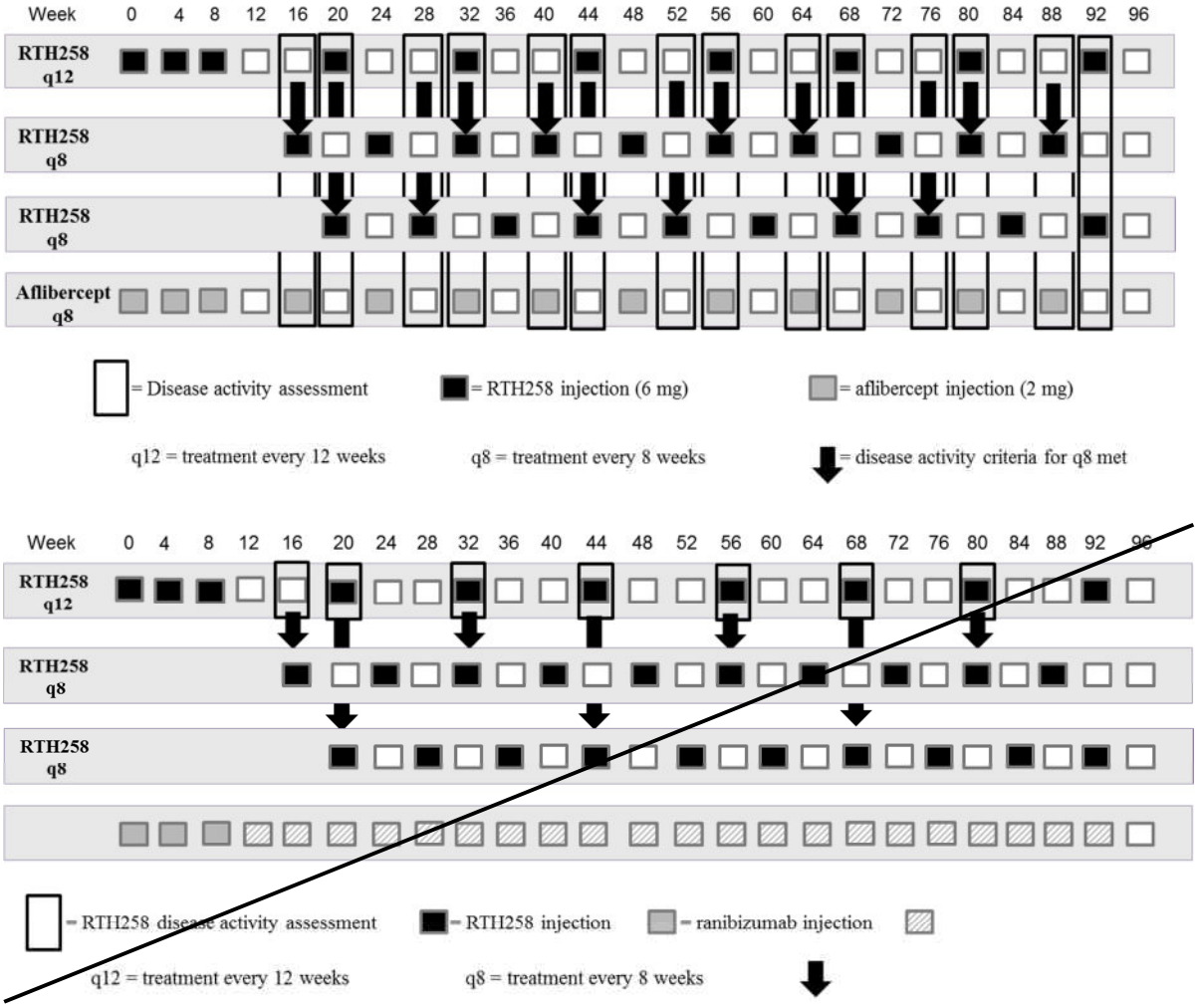
Disease Activity Criterion at Weeks 52, 56, 64, 68, 76, 80, 88 and 92:

- Decrease in BCVA of ≥ 5 letters due to neovascular AMD disease activity compared with Week 48

A subject randomized to RTH258 6 mg who misses Visit 5/Week 16, Visit8/Week 28, Visit 11/Week 40, Visit14/Week 52, Visit 17/Week 64, Visit 20/Week 76 and/or Visit 23/Week 88 will undergo the disease activity assessment at the next scheduled visit ~~Visit 6/Week 20~~ as he/she would have done if the visit had not been missed. If, however, a subject randomized to RTH258 6 mg misses any of the following disease activity assessment visits (Visit 6/Week 20, Visit 9/Week 32, Visit 12/Week 44, Visit 15/Week 56, Visit 18/Week 68 or Visit 21/Week 80) then the subject will be assumed to have met the disease activity criterion at the missed visit and will be reassigned to a q8 regimen up to study exit. The IRT system will make the necessary changes once the missed visit is registered.

Figure 10.1-1 Dose schedule by treatment

Figure 10.1.-1
Dosing schedule by treatment



Section 10.2.4 Visit 4/Week 12 (Day 84 ± 7 days) through Visit 24/Week 92 (Day 644 ± 7 days)

16. Have the masked Investigator perform the visit appropriate disease activity assessment for the study eye (*Visit 5, Visit 6, Visit 8, Visit 9, Visit 11, Visit 12, Visit 14, Visit 15, Visit 17, Visit 18, Visit 20, Visit 21, Visit 23 and Visit 24*).

Section 10.5 Discontinuation of Study Treatment

The Investigator may discontinue study treatment for a given subject and/or withdraw the subject from study if he/she believes that continuation would pose a risk to their health. Subjects can be discontinued from study treatment because of

- appearance of a new health condition suspected to require appropriate care or require medications prohibited by the protocol
- refusal to continue treatment, or at the Investigator's discretion based on his/her clinical judgement the subject requires rescue medication
- use of prohibited treatment during the study
- investigator's discretion based on his/her clinical judgment
- positive urine/serum pregnancy test

Section 10.6 Clinical Study Termination

The Investigator also may terminate the study at his/her site for reasonable cause. If the Sponsor terminates the study for safety reasons, it will immediately notify the Investigator(s) by telephone and subsequently will provide written confirmation of and instructions for study termination. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the IRBs/IECs of the early termination of the trial.

Section 10.7.13 Disease Activity Assessment

The masked Investigator will assess the study eye of all subjects at Visit 5/Week 16, Visit 6/Week 20, Visit 8/Week 28, Visit 9/Week 32, Visit 11/Week 40, Visit 12/Week 44, Visit 14/Week 52, Visit 15/Week 56, Visit 17/Week 64, Visit 18/Week 68, Visit 20/Week 76, Visit 21/Week 80 and Visit 23/Week 88. The IRT system will make the necessary changes to the dosing per the masked Investigator's assessment. The disease activity assessment will also be performed at Visit 24/Week 92, but will not be entered into IRT, and will have no effect on the subject's treatment regimen. Details of the disease activity assessments are further outlined in the MOP.

Section 10.7.4 Laboratory Analysis of Blood and Urine

Blood and urine samples will be shipped to a central laboratory. Results of the analysis will be provided to the Investigator who will assess those from Screening prior to randomizing the subject to determine if there is anything that would preclude participation of the subject and at subsequent visits to assess any changes from Screening. A standardized procedure for the collection and processing of blood and urine is provided by the central laboratory. A list of laboratory parameters is provided in the MOP. If a subject should present with a clinically significant change resulting in an adverse event, as assessed by the Investigator, a decision will be made by the Investigator and Sponsor as to subject continuation in the trial. This decision will take into account the adverse event characteristics including but not limited to seriousness and relationship to study drug.

Section 11 Analysis Plan

Section 11.5 Primary and Key Secondary Efficacy Analyses

The primary and first key secondary endpoints will be analyzed based on the FAS with last-observation-carried-forward (LOCF) imputation of missing BCVA values (primary and first key secondary endpoint) and a negative q12 treatment status at Week 48 in the case of incomplete active treatment up to Week 48 (second and third key secondary endpoint). The analysis of the primary and key secondary endpoints based on the PPS will be considered supportive. 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 data sets.

Section 11.5.2 Statistical Methods

The q12 treatment status of subjects in the RTH258 6 mg treatment arm will be presented descriptively together with exact 95% confidence intervals for the proportion of subjects with a positive status.

- For the overall proportion of subjects with a positive q12 treatment status at week 48, the denominator is all FAS subjects in the RTH258 6 mg group, and the numerator is the corresponding number of subjects with no identified need for treatment at q8 at Week 16, 20, 28, 32, 40 and 44 (while missing Week 16, Week 28 and/or Week 40 assessment is considered as no q8 treatment needed)

- For the predictability of the adequacy of q12 treatment, based on the absence of disease activity during the first q12 cycle, the denominator is all FAS subjects in the RTH258 6 mg group with no identified need for treatment q8 at Week 16 and Week 20 (while missing Week 16 assessment is considered as no q8 treatment needed), and the numerator is the corresponding number of subjects with a positive q12 treatment status at Week 48, i.e., with no identified need for treatment at q8 at Week 16, 20, 28, 32, 40 and 44 (while missing Week 16, Week 28 and/or Week 40 assessment is considered as no q8 treatment needed)

Section 11.6 Additional Secondary Efficacy Analyses

The following secondary efficacy endpoints will be analyzed primarily based on the FAS:

- 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
- ~~Average change in BCVA from Baseline over the period Week 48 through Week 96~~
- Gain in BCVA of 15/10/5 letters or more from Baseline to each postbaseline 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 6 mg only)
- q12 treatment status at Week 96 within the subjects with no q8-need during the 1st q12 cycle (ie, at Week 16 and Week 20) (for subjects randomized to RTH258 6 mg only)
- Change in CSFT from Baseline to each postbaseline visit
- Change in neurosensory retinal thickness from Baseline to each postbaseline visit
- Change in CNV lesion size from Baseline to Weeks 12, 48 and 96
- Absence of subretinal fluid at each visit
- Absence of intraretinal fluid at each visit
- q8 treatment need status assessed at Weeks 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88 and 92
- Change in patient reported outcomes (VFQ-25) total and subscale scores from Baseline to Weeks 24, 48, 72 and 96

Section 12 Safety

12.3 Procedures for Recording and Reporting AEs and SAEs

In addition to the reporting of SAEs to the Sponsor, the SAE must be reported to the IEC / IRB according to their requirements. In addition, SAEs will be reported to regulatory agencies based upon local reporting requirements.

If the SAE is not previously documented in the Investigator's Brochure and is thought to be related to the investigational treatment the Sponsor may urgently require further information from the investigator for Health Authority reporting. Sponsor may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

If the SAE was due to a hospitalization of the subject, a copy of the discharge summary is to be forwarded to the Sponsor as soon as it becomes available. In addition, a letter from the Investigator that summarizes the events related to the case as well as results of any relevant laboratory tests may also be requested. Further, depending upon the nature of the SAE, the Sponsor may request copies of applicable portions of the subject's medical records.

Section 12.7 Pregnancy in the Study

Women of childbearing potential are not excluded from the study as long as adequate birth control methods are being utilized or women considered post-menopausal. Women of childbearing potential are defined as fertile ~~as all women~~ and physiologically capable of becoming pregnant, following menarche and until becoming post-menopausal unless permanently sterile. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. All women of childbearing potential are required to use ~~A~~adequate birth control methods which are

summarized in the protocol's exclusion criteria and should be used during the study and continued up to 3 months post final study injection.

Section 13 Data Handling and Administrative requirements

Section 13.5 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established to monitor the safety of the trial participants, to ensure that the trial is being conducted with the highest scientific and ethical standards, and make appropriate recommendations based on the data seen.

The DMC charter will include the DMC membership and responsibilities, the timing of DMC meetings, the content of the analysis report for the DMC meetings, and the communication with the Sponsor. The DMC will only make recommendations for changes in study conduct.

2 OVERVIEW OF STUDY PLAN

	Screening	Visit 1/ Baseline	Visit 2/ Week 4	Visit 3/ Week 8	Visit 4/ Week 12	Visit 5/ Week 16	Visit 6/ Week 20	Visit 7/ Week 24	Visit 8/ Week 28	Visit 9/ Week 32	Visit 10/ Week 36	Visit 11/ Week 40	Visit 12/ Week 44	Visit 13/ Week 48
	Day -14 to -2	Day 0	Day 28 ± 3 Days	Day 56 ± 3 Days	Day 84 ± 7 Days	Day 112 ± 7 Days	Day 140 ± 7 Days	Day 168 ± 7 Days	Day 196 ± 7 Days	Day 224 ± 7 Days	Day 252 ± 7 Days	Day 280 ± 7 Days	Day 308 ± 7 Days	Day 336 ± 7 Days
Informed Consent[1]	X													
Demographics	X													
Medical History /Concomitant Medications	X													
Changes in Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X
Monitor for Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X	X[2]												
Visual Function Questionnaire-25 (VFQ-25)[3]		X						X						X
General Physical Exam[4]	X													X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[5]	X													X
Blood/Urine Sample: Chemistry/ Hematology/ Urinalysis[6]	X				X									X

	Screening	Visit 1/ Baseline	Visit 2/ Week 4	Visit 3/ Week 8	Visit 4/ Week 12	Visit 5/ Week 16	Visit 6/ Week 20	Visit 7/ Week 24	Visit 8/ Week 28	Visit 9/ Week 32	Visit 10/ Week 36	Visit 11/ Week 40	Visit 12/ Week 44	Visit 13/ Week 48
	Day -14 to -2	Day 0	Day 28 ± 3 Days	Day 56 ± 3 Days	Day 84 ± 7 Days	Day 112 ± 7 Days	Day 140 ± 7 Days	Day 168 ± 7 Days	Day 196 ± 7 Days	Day 224 ± 7 Days	Day 252 ± 7 Days	Day 280 ± 7 Days	Day 308 ± 7 Days	Day 336 ± 7 Days
Blood Draw for Anti-Drug Antibodies (ADA)[6]		X			X			X			X			X
Blood Draw for Systemic RTH258[6]		X			X			X			X			X
Blood Draw for Genetics[6]		X												
Best-Corrected Visual Acuity (BCVA)[7]	X[8]	X[8]	X	X	X[8]	X	X	X[8]	X	X	X[8]	X	X	X[8]
Complete Ophthalmic Exam[9]	X[8]	X	X	X	X	X	X	X	X	X	X	X	X	X[8]
Spectral Domain Optical Coherence Tomography (SD-OCT)	X[8]	X	X	X	X	X	X	X	X	X	X	X	X	X[8]
Fluorescein Angiography (FA)[10]	X[8]				X									X[8]
Color Fundus Photography	X[8]				X									X[8]
Fundus Autofluorescence (FAF)[11]		X[11]			X[11]									X[11]
Disease Activity Assessment						X	X		X	X		X	X	

	Screening	Visit 1/ Baseline	Visit 2/ Week 4	Visit 3/ Week 8	Visit 4/ Week 12	Visit 5/ Week 16	Visit 6/ Week 20	Visit 7/ Week 24	Visit 8/ Week 28	Visit 9/ Week 32	Visit 10/ Week 36	Visit 11/ Week 40	Visit 12/ Week 44	Visit 13/ Week 48
	Day -14 to -2	**Day 0**	**Day 28 ± 3 Days**	**Day 56 ± 3 Days**	**Day 84 ± 7 Days**	**Day 112 ± 7 Days**	**Day 140 ± 7 Days**	**Day 168 ± 7 Days**	**Day 196 ± 7 Days**	**Day 224 ± 7 Days**	**Day 252 ± 7 Days**	**Day 280 ± 7 Days**	**Day 308 ± 7 Days**	**Day 336 ± 7 Days**
Contact Interactive Response Technology (IRT)	X	X	X	X		X	X	X	X	X	X	X	X	X
Administer Study Injection or Sham[12]/ Post- Injection Assessment[13]		X	X	X		X	X	X	X	X	X	X	X	X

	Visit 14/ Week 52	Visit 15/ Week 56	Visit 16/ Week 60	Visit 17/ Week 64	Visit 18/ Week 68	Visit 19/ Week 72	Visit 20/ Week 76	Visit 21/ Week 80	Visit 22/ Week 84	Visit 23/ Week 88	Visit 24/ Week 92	Visit 25/ Week 96 Exit[14]
	Day 364 ± 7 Days	Day 392 ± 7 Days	Day 420 ± 7 Days	Day 448 ± 7 Days	Day 476 ± 7 Days	Day 504 ± 7 Days	Day 532 ± 7 Days	Day 560 ± 7 Days	Day 588 ± 7 Days	Day 616 ± 7 Days	Day 644 ± 7 Days	Day 672 ± 7 Days
Changes in Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Monitor for Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Visual Function Questionnaire-25 (VFQ-25)[3]						X						X
General Physical Exam[4]												X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[5]												X
Blood/Urine Sample: Chemistry/ Hematology/ Urinalysis[6]												X
Blood Draw for Anti-Drug Antibodies (ADA)[6]					X					X		(X)[15]
Blood Draw for Systemic RTH258[6]					X					X		(X)[15]
Blood Draw for Genetics[6]												

	Visit 14/ Week 52	Visit 15/ Week 56	Visit 16/ Week 60	Visit 17/ Week 64	Visit 18/ Week 68	Visit 19/ Week 72	Visit 20/ Week 76	Visit 21/ Week 80	Visit 22/ Week 84	Visit 23/ Week 88	Visit 24/ Week 92	Visit 25/ Week 96/ Exit[14]
	Day 364 ± 7 Days	Day 392 ± 7 Days	Day 420 ± 7 Days	Day 448 ± 7 Days	Day 476 ± 7 Days	Day 504 ± 7 Days	Day 532 ± 7 Days	Day 560 ± 7 Days	Day 588 ± 7 Days	Day 616 ± 7 Days	Day 644 ± 7 Days	Day 672 ± 7 Days
Best-Corrected Visual Acuity (BCVA)	X	X	X8	X	X	X8	X	X	X8	X	X	X
Complete Ophthalmic Exam [9]	X	X	X	X	X	X	X	X	X	X	X	X[8]
Spectral Domain Optical Coherence Tomography (SD-OCT)	X	X	X	X	X	X	X	X	X	X	X	X[8]
Fluorescein Angiography (FA)[10]												X[8]
Color Fundus Photography												X[8]
Fundus Autofluorescence (FAF)[11]												X[11]
Disease Activity Assessment	X	X		X	X		X	X		X	X	
Contact Interactive Response Technology (IRT)	X	X	X	X	X	X	X	X	X	X	X	
Administer Study Injection or Sham[12]/ Post- Injection Assessment[13]	X	X	X	X	X	X	X	X	X	X	X	
Complete Exit Form												X

1. The informed consent form must be signed/dated prior to performing any study procedures, including screening procedures.
2. Verify that inclusion/exclusion criteria are met at Visit 1/Baseline prior to assignment of study treatment.
3. Questionnaires are to be administered at those sites where validated translations are available and where they are approved by the corresponding Independent Ethics Committee/Institutional Review Board (IEC/IRB). Questionnaire must be administered prior to any examination.
4. All clinically significant findings will be recorded as medical history or adverse events, as appropriate.
5. Required for all female subjects of childbearing potential. Urine pregnancy tests will be performed unless local regulations require a serum pregnancy test.
6. All blood draws and collection of urine should be performed prior to receiving the IVT or sham injection and prior to injection of fluorescein dye
7. BCVA must be performed at the Screening and at the Baseline Visit to qualify the subject.
8. Both eyes; all other assessments are study eye only.
9. Includes slit-lamp exam, IOP measurement, and fundus exam. Dilation for the fundus exam is at the discretion of the Investigator.
10. Other FA assessments, done outside of visit schedule, may be performed at Investigator's discretion based on exam findings, observations, etc.
11. FAF will be performed at a subset of sites.
12. Subjects will be randomized to one of the following treatments: RTH258 6 mg or aflibercept 2 mg. Beginning at Week 16, when subjects do not receive an active injection, they will receive a sham injection. The injection may be performed at a later time, as long as it is within 7 days of the scheduled visit and within the visit window.
13. Whether the subject receives an active injection or sham injection, the study eye will be evaluated 0-5 minutes and 30 (±15) minutes postinjection to ensure that the injection procedure and/or the investigational product have not endangered the health of the eye. This evaluation includes an evaluation of central retinal artery perfusion via gross assessment of vision and measurement of IOP. Direct visualization to assess the central retinal artery, presence of retinal detachment, presence of new intraocular hemorrhage(s) might be appropriate at the discretion of the investigator and/or based on the results of gross assessment of vision and IOP measurement).
14. All exit procedures should be followed, regardless of when the subject exits the study.
15. Blood draws for ADA and systemic RTH258 will be performed if the subject exits at or before Visit 23/Week 88.

3 ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AEF	Adverse event form
AMD	Age-related macular degeneration
ANOVA	Analysis of variance
BCVA	Best-corrected visual acuity
CI	Confidence interval
CNV	Choroidal neovascularization
CRC	Central reading center
CRF	Case report form
CSFT	Central subfield thickness
CSM	Clinical site management
CTM	Clinical trial management
DEP	Deviations and evaluability plan
EDC	Electronic data capture
ESI	Event of special interest
ETDRS	Early treatment diabetic retinopathy study
FA	Fluorescein angiography
FAF	Fundus autofluorescence
FAS	Full analysis set
GCP	Good clinical practice
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional review board
IRC	Intraretinal cysts
IRF	Intraretinal fluid
IRT	Interactive response technology
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine system
IVT	Intravitreal
LOCF	Last observation carried forward
Mg	Milligram
mL	Milliliter

Abbreviation	Definition
mmHg	Millimeters of mercury
MMRM	Mixed model repeated measures
MOP	Manual of procedures
PPS	Per protocol analysis set
PRN	*Pro re nata*
q8	Every 8 weeks
q12	Every 12 weeks
RAP	Retinal angiomatous proliferation
RPE	Retinal pigment epithelium
SAE	Serious adverse event
SAP	Statistical analysis plan
scFv	Single chain variable fragment
SD-OCT	Spectral-domain optical coherence tomography
SUSAR	Suspected unexpected serious adverse reaction
µL	Microliter
VEGF	Vascular endothelial growth factor
VFQ-25	Visual Function Questionnaire

3.1 Glossary of terms

Term	Definition
AMD	Clinical and/or angiographic signs of retinal degeneration (including drusen, hypo- or hyper-pigmentation, geographic atrophy, and choroidal neovascularization) with no other likely etiologic explanations for the degenerative changes
CNV (subfoveal) secondary to AMD	Angiographic evidence of new blood vessel growth within the central subfield. The lesion containing the new vessel growth may be classic and/or occult and can include thick contiguous blood or an area of elevated blocked fluorescence corresponding to pigment that obscures the boundaries of the neovascular components, or serous detachment of the retinal pigment epithelium
Central subfield	The circular area within 1 mm diameter around the foveal center on imaging

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5 INTRODUCTION

5.1 Study Rationale and Background

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in people affecting 10%-13% of individuals over the age of 65 in North America, Europe, and Australia (Kawasaki 2010, Rein 2009, Smith 2001). Genetic, environmental and health factors play an important role in the pathogenesis of the disease.

AMD is classified into 2 clinical subtypes: the non-neovascular (atrophic) or dry form and the neovascular (exudative) or wet form (Ferris 1984, Lim 2012, Miller 2013). Neovascular AMD is characterized by the growth of abnormal new blood vessels (neovascularization) under the retinal pigment epithelium (RPE) or subretinal space from the subjacent choroid, termed choroidal neovascularization (CNV) (Ferris, 1984). These newly formed vessels have an increased likelihood to leak blood and serum, damaging the retina by stimulating inflammation and scar tissue formation. This damage to the retina results in progressive, severe, and irreversible vision loss (Shah 2007, Shah 2009). Without treatment, most affected eyes will have poor central vision (20/200) within 12 months (TAP 2003). Although the neovascular form of the disease is only present in about 10% of all AMD cases, it accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (VEGF) treatments (Ferris 1983, Sommer 1991, Wong 2008).

VEGF has been shown to be elevated in patients with neovascular AMD, and is thought to play a key role in the neovascularization process (Spilsbury 2000). The use of intravitreal (IVT) pharmacotherapy targeting VEGF has significantly improved visual outcomes in patients with neovascular AMD (Bloch 2012, Campbell 2012). Anti-VEGF treatments, such as ranibizumab (LUCENTIS) and aflibercept (EYLEA), inhibit VEGF signaling pathways and have been shown to halt the growth of neovascular lesions and resolve retinal edema.

Ranibizumab

In two Phase 3 studies of ranibizumab with monthly dosing regimens, approximately 95% of ranibizumab treated subjects experienced stabilization of vision (defined as a loss of fewer than 15 early treatment diabetic retinopathy study [ETDRS] letters) or improvement in vision at 12 months compared with 62% and 64% in the control groups (Rosenfeld 2006, Brown 2009). Twenty-five to 40% of subjects in the ranibizumab groups gained ≥ 15 letters at 12 months compared with 5-6% in the 2 control groups. On average, ranibizumab treated subjects gained 7-11 letters of vision after 12 months, whereas control subjects lost an

average of approximately 10 letters. This gain in visual acuity was essentially maintained during the second year of both Phase 3 studies while vision, on average, continued to decline in the control group. The visual acuity benefits, which indicate a suspension of neovascular AMD rather than a slowdown of its progression, were supported by corresponding effects on lesion anatomy and subject reported outcomes. The latter demonstrated statistically and clinically meaningful improvements in near activities, distance activities, and vision specific dependency as measured by the National Eye Institute Visual Function Questionnaire-25 (VFQ-25).

Aflibercept

In two parallel Phase 3 trials of aflibercept, treatment naïve subjects with neovascular AMD were randomized to 2 doses (0.5 and 2.0 mg) and 2 regimens (every 4 weeks and every 8 weeks with 2.0 mg) or the control arm (ranibizumab 0.5 mg every 4 weeks). At 52 weeks, all aflibercept groups, independent of doses and regimens, were noninferior to the ranibizumab group with equal stabilization of vision in 95% of eyes (Heier 2012). In the 2 mg aflibercept every 4 weeks group, there was a mean best-corrected visual acuity (BCVA) improvement of 9.3 letters and in the 2 mg aflibercept every 8 weeks group there was an improvement of 8.4 letters compared to the control group which had a mean improvement of 8.7 letters. In the second year of the study subjects were switched to a capped (treatment required at least every12 weeks) *pro re nata* (PRN) regimen. The proportion of subjects who maintained BCVA ranged between 91% and 92% for all groups. Mean BCVA improvements ranged from 7.9 (ranibizumab), 7.6 (aflibercept 2 mg every 4 weeks and every 8 weeks) to 6.6 (aflibercept 0.5 mg every 4 weeks). The retreatment frequency was similar between the aflibercept and ranibizumab arms during the capped PRN year, with a mean of 4.1 injections for the aflibercept 2 mg every 4 weeks arm, 4.2 injections for the aflibercept 2 mg every 8 weeks arm and 4.7 for the ranibizumab arm (Schmidt-Erfurth 2014).

RTH258

RTH258, formerly known as ESBA1008, is a humanized single-chain Fv (scFv) antibody fragment inhibitor of VEGF with a molecular weight of ~26 kDa that is being developed for the treatment of CNV associated with neovascular AMD. It is an inhibitor of VEGF-A and works by binding to the receptor binding site of the VEGF-A molecule, thereby preventing the interaction of VEGF-A with its receptors VEGFR1 and VEGFR2 on the surface of endothelial cells. Increased levels of signaling through the VEGF pathway are associated with pathologic ocular angiogenesis and retinal edema. Inhibition of the VEGF pathway has

been shown to inhibit the growth of neovascular lesions and resolve retinal edema in patients with neovascular AMD.

In an ascending single dose study, Alcon protocol C-10-083, several doses of RTH258 (0.5, 3.0, 4.5 and 6 mg), were evaluated versus ranibizumab 0.5 mg with regard to the mean change from Baseline to Month 1 in central subfield thickness (CSFT) as measured by spectral- domain optical coherence tomography (SD-OCT) (primary efficacy endpoint). Treatment with RTH258 provided similar reductions for all doses in CSFT to ranibizumab. The primary statistical analysis compared RTH258 4.5 mg and 6.0 mg versus ranibizumab 0.5 mg with both doses achieving non-inferiority. Notable however was the median time to receiving standard of care which was 45.0 days for ranibizumab but was longer for the RTH258 3.0 mg, 4.5 mg and 6.0 mg doses (75.0 days(p=0.0374), 60.0 days (p=0.1805) and 75.0 days (p=0.0360) respectively). The interquartile range was 30 – 75 days for ranibizumab, and 45 – 120 days, 30 – 120 days and 37.5 – 150 days for the RTH258 3.0 mg, 4.5 mg and 6.0 mg respectively. RTH258 6 mg was the highest dose tested in the study and no unexpected safety issues were reported that would preclude further clinical development.

Subsequently the safety and efficacy of the RTH258 6 mg dose were evaluated versus aflibercept 2 mg in a 56 week multiple dose study (Alcon protocol C-12-006) with a primary endpoint at 12 weeks. The efficacy data from this study showed that RTH258, when it was given every 8 weeks (q8), was as effective as the active control in terms of BCVA change from Baseline. There were numerical advantages with RTH258 over aflibercept with regard to the change in CSFT from Baseline. The majority (72%) of the RTH258 treated subjects who completed an extension of the study, who received treatment every 12 weeks (q12), showed visual stability. There were no adverse events in the RTH258 group that negatively differentiated the drug from the control. The majority of adverse events were mild or moderate in nature and either resolved spontaneously or with treatment.

5.1.1 Dose Rationale

Studies C-10-083 and C-12-006 suggest that a 6 mg dose of RTH258 is effective and safe.

5.1.2 Treatment Regimen Rationale

While VEGF inhibitors have vastly improved patient outcomes for neovascular AMD, there still remains a need for treatments and regimens which offer a reduced frequency of injections. Frequent treatment and monitoring schedules remain a significant burden to patients, caregivers and physicians. The proposed Phase 3 study aims to address these.

In the current study, RTH258 patients will receive q12 maintenance dosing. Disease activity assessments will be conducted by a masked investigator at Weeks 16, 20, 28, 32, 40 and 44, allowing 6 time points up to the primary endpoint of the study (Week 48) where RTH258 q12 subjects can be reassigned to q8 treatment. It is expected that early determination at Week 16 and Week 20 of subjects who are more suited to a q8 dosing regimen will minimize the percentage of q12 subjects who will require reassignment at later time points.

Analyses from the PIER (Regillo 2008) and EXCITE (Schmidt-Erfurth 2011) studies have shown that visual and anatomic response during, and for the 12 weeks after the loading phase, are associated with visual acuity outcomes over the remainder of the first year of treatment. In addition, recent analyses from the EXCITE (Chong 2013) study have also shown that subjects who lose vision during the initial loading phase will have better visual outcomes with more frequent treatment versus q12 treatment. Finally, analyses from CATT (Kim 2014, Ying 2014) and EXCITE (Simader 2014) have also shown that new intraretinal fluid (IRF)/intraretinal cysts (IRC), and to a lesser degree CSFT increase, are associated with later visual acuity decline.

Due to the well-established efficacy of anti-VEGF treatments in the indication of neovascular Age-Related Macular Degeneration, an internal validation of this study via a placebo arm is ethically not feasible. The available historical evidence of the efficacy of Lucentis (Anchor and Marina) and of aflibercept (VIEW 1 and 2) allows for a reliable estimate of the drug's effect size compared to placebo and due to the similarity of the current NI trial to the historical studies in terms of study population, efficacy assessments and duration, there is a sound basis for external validation of the results of this study.

5.1.3 Non-inferiority Margin Rationale

Non-inferiority testing related to the primary efficacy parameter best corrected visual acuity [letters] will be based on a margin of 4 letters. This non-inferiority margin provides assurance that both absolute efficacy and acceptable efficacy relative to the active comparator aflibercept can be established.

- Absolute efficacy: The active comparator aflibercept together with Lucentis belongs to a class of anti-VEGF treatments where for the individual products similar efficacy has been established (VIEW 1 and 2). This similarity justifies the use of the only available related superiority data versus Sham or Visudyne reported for monthly Lucentis in the studies MARINA (vs Sham) and ANCHOR (vs Visudyne) to quantify the order of magnitude of the absolute treatment effect for this class of treatments. For the endpoint 'change in BCVA from baseline to Month 12 [letters]' this absolute treatment effect was estimated for monthly Lucentis 0.5mg in the MARINA study as 17.5 letters (95%CI [14.8 , 20,2]) compared to Sham-injections and in the ANCHOR study as 21.1 letters (95% CI [17.5 , 24.6]) compared to Visudyne . Relative to these absolute treatment effects, non-inferiority established at a 4 letter margin will guarantee an absolute treatment effect in the magnitude of at least 10 letters even under the conservative approach of using the lower limits of these 95% confidence intervals as reference.

- Establishing acceptable efficacy relative to the active comparator aflibercept: For a non-inferiority margin of 4 letters together with the assumed standard deviation of 15 letter for the primary endpoint BCVA change from baseline at Week 48 and a sample size of 300 patients, it is expected that non-inferiority can only be claimed if the observed difference between RTH258 and aflibercept is > -1.6 letters. Signifying that the observed mean BCVA change for RTH258 is no more than 1.6 letters worse than for aflibercept.

  The power calculation is based on the assumption of equal efficacy for RTH258 and aflibercept with a resulting power of about 80% for two successful Phase III studies, while in case of a real treatment difference of -1.6 letters the power goes down to 25%. Even if the treatment difference is only -1 letter, the chance for two successful Phase III studies falls below 50%.

  While a 4 letter difference in the BCVA response between two regimens can be considered of relevance, a 4 letter non-inferiority margin in a clinical trial leads to a discrimination of treatments already for much smaller delta-levels for which minor underlying clinical relevance can be attributed.

5.2 Benefits and Risks

RTH258 is an inhibitor of VEGF with a mechanism of action similar to ranibizumab but with a smaller molecular size (26 kDa and 48 kDa respectively).

Nonclinical studies have demonstrated that RTH258 is at least as potent as ranibizumab, with a similar vitreal half-life and a significantly lower systemic exposure. The low systemic exposure should confer a good safety profile even at a high dose. The higher dose, similar

half-life, and potency of RTH258 may confer a longer treatment duration compared to currently available treatments. Two clinical studies, C-10-083 and C-12-006, have demonstrated that RTH258 is as effective as ranibizumab and aflibercept in improving BCVA outcomes whilst having a reduced treatment frequency, thus providing a potential benefit to patients and their caregivers/physicians. The ocular and systemic safety profile of single or repeated doses of RTH258 were also evaluated in the C-10-083 and C-12-006 studies, respectively, and demonstrated similar safety profiles to ranibizumab and aflibercept. Further details of the known and potential risks and benefits associated with RTH258 are presented in the Investigator's Brochure.

Summarized, the results from the Phase 2 studies demonstrate that RTH258 has similar efficacy to currently available treatment options with potentially greater duration of effect. These data support the further development of RTH258 with a treatment regimen including q12 maintenance dosing.

6 ETHICS

This clinical study will be conducted in accordance with the principles of the Declaration of Helsinki, and in compliance with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline and other regulations as applicable. The Investigator and all clinical study staff will conduct the clinical study in compliance with the protocol. The Investigator will ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience.

Before clinical study initiation, this protocol, the informed consent form (and assent form, if applicable), any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB). The Investigator must provide documentation of the IEC/IRB approval to the Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, assent form (if any), all applicable recruiting materials, written information for subject, and subject compensation programs. The IEC/IRB must be provided with a copy of the Investigator's Brochure, any periodic safety updates, and all other information as required by local regulation and/or the IEC/IRB. At the end of the study, the Investigator will notify the IEC/IRB about the study's completion. The IEC/IRB also will be notified if the study is terminated prematurely. Finally, the Investigator will report to the IEC/IRB on the progress of the study at intervals stipulated by the IEC/IRB.

Voluntary informed consent will be obtained from every subject (and/or legal representative, as applicable) prior to the initiation of any screening or other study-related procedures. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or designee, will explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The subject must be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel. The Investigator must provide the subject with a copy of the consent form written in a language the subject understands. The consent document must meet all applicable local laws and will provide subjects with information regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with the investigational product, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Subjects will be told about the voluntary nature of participation in the study and will be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject also will be told that their

records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator must keep the original, signed copy of the consent and must provide a duplicate copy to each subject.

7 PROTOCOL AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments will be created by the Sponsor and must be approved by the IEC/IRB and Regulatory Authorities prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Amendments may necessitate that the ICF and other study-related material be revised. If the ICF is revised, all subjects currently enrolled in the study may be required by the IEC/IRB to sign the approved, revised ICF.

8 SUBJECT POPULATION

The study population includes approximately 660 subjects to be randomized at approximately 200 sites. To participate in the study, subjects must be ≥ 50 years of age with untreated active CNV secondary to AMD in the study eye. The expected duration of subject participation in the randomized portion of the study is 96 weeks. The complete inclusion and exclusion criteria are presented in Section 1.

9 TREATMENTS ADMINISTERED

At Visit 1/Baseline Visit (Day 0), all eligible subjects will be randomized centrally using Interactive Response Technology (IRT) in a 1:1 ratio to receive either RTH258 6 mg/50 µL or aflibercept 2 mg/50 µL. In the event that IRT is not available for randomization, the site should contact the Sponsor about how to proceed. In these cases subjects may be manually randomized.

Throughout the study, the Investigator will be responsible for the accounting of all study materials and investigational products, and will ensure that the investigational products are not used in any unauthorized manner.

9.1 Identity of Study Treatments

Test Article: *RTH258 solution for IVT injection, 6 mg in 50 µL* (120 mg/mL formulation)
Control Article: *Aflibercept solution for IVT injection, 2 mg in 50 µL*

The trial kits will consist of a carton that contains 1 single use, sterile glass vial containing RTH258 6 mg or aflibercept 2 mg.

Kit labels on all trial kits include the kit number, protocol number, storage conditions, and a statement that the product is for investigational use only.

All trial kits should be stored at 2º to 8ºC (35.6º to 46.4ºF); do not freeze. To ensure proper conditions are maintained, a daily (7 days/week) temperature log will be maintained documenting appropriate investigational product storage conditions.

9.2 Usage

RTH258 6 mg will be administered by IVT injection. All doses will be delivered in 50 µL (0.05 mL). Subjects in the RTH258 6 mg arm will receive loading doses at Visit 1/Day 0, Visit 2/Week 4 and Visit 3/Week 8. After the loading doses subjects will receive q12 treatment unless there is disease activity according to the guidance provided in Section 10.1.

If disease activity is identified, the subject will be reassigned to receive injections q8 thereafter, up to Visit 24/Week 92.

Aflibercept 2 mg will be administered as a 50 µL (0.05 mL) IVT injection. Subjects randomized to receive aflibercept will receive loading doses at Visit 1/Day 0, Visit 2/Week 4 and Visit 3/Week 8 followed by injections q8 to Visit 24/Week 92.

To maintain masking, beginning at Visit 6/Week16, if a subject should not receive an active treatment, a sham injection will be performed.

If at any visit, a subject is accidentally treated with investigational product (IP) from the arm other than the one to which they were assigned, they will be treated with the IP they were randomized to by IRT, and follow the treatment schedule of that arm for the remainder of the study. In the event this occurs, it must be reported to the Sponsor immediately.

9.3 Accountability Procedures

Each site must have designated unmasked site personnel who, upon receipt of the IP, will conduct an inventory. At the appropriate study visits, designated unmasked study staff will provide the IP to the unmasked injecting physician in accordance with the IRT procedures.

During the study, the Investigator must maintain records of IP dispensation and collection for each subject. This record must be made available to the unmasked study monitor for the purposes of verifying the accounting of clinical supplies. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation. At the conclusion of the study, the Investigator will be responsible for returning all used and unused study supplies unless otherwise instructed by the Sponsor.

9.4 Subject Confidentiality and Methods Used to Minimize Bias

The Investigator must ensure that the subject's anonymity is maintained throughout the course of the study. In particular, the Investigator must keep an enrollment log with confidential identifying information that corresponds to the subject number of each study participant. At the end of the clinical study, the Sponsor will collect a copy of the enrollment log without any identifying subject information. All documents submitted to the Sponsor will identify the subject exclusively by number and demographic information. No other personally identifying information should be transmitted to the Sponsor.

The intent of masking is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. The essential aim of masking, therefore, is to prevent identification of the treatments by the Investigator, subject, and others associated with the conduct of the study until all such opportunities for bias have passed.

This study will be double-masked, with subjects randomized to be treated with RTH258 6 mg or aflibercept 2 mg. All members of the Clinical Study Team will be masked to treatment assignments while the study is in progress. In addition, the biostatistician who is directly involved in the conduct of the study (i.e. involved in patient level discussions or direct

interaction with sites) will remain masked to treatment assignments while the study is in progress. Sponsor personnel who have access to treatment codes (eg, SAS Programming personnel directly involved with bioanalysis of serum samples, unmasked monitors performing IP accountability, and Clinical Supplies personnel) will not divulge the codes to subjects, Investigators, site staff, Sponsor Clinical Trial Management (CTM), or Sponsor Clinical Site Management (CSM). If necessary, the Sponsor may be required to unmask a subject if an adverse event (AE) meets criteria of a Suspected Unexpected Serious Adverse Reaction (SUSAR) in order to fulfill expedited regulatory reporting requirements. In this event, the Sponsor Safety Review Team will not divulge the treatment code to any other personnel involved in reporting, obtaining, and/or reviewing the clinical evaluations. This level of masking will be maintained throughout the conduct of the study.

Each site must have both masked and unmasked physicians available. The physician who performs the injection will be unmasked to the treatments as will any other site personnel who have been delegated responsibility for working with the IP. The unmasked site personnel and unmasked injecting physician must not perform any study assessments which may compromise the efficacy (ie, BCVA, complete ophthalmic examination, disease activity assessments or administer the VFQ-25). Also, the unmasked site personnel and unmasked injecting physician must not perform assessment of any ocular or nonocular safety parameters, or assess causality AEs for subjects during the course of the study except an event reported immediately following IVT injection. The unmasked physician/site personnel should, however, assess subject safety immediately following injection (ie, they will perform the postinjection assessment; the masked physician/site personnel should not perform this assessment). Unmasked monitors will be provided to perform IP accountability.

Treatment will be assigned to subjects through the IRT system. Each subject number will be associated with treatment groups according to a random process generated using computer software (SAS 9.2 PROC PLAN). Subjects will be assigned in sequence number order according to time of randomization; the randomization schedule will be blocked to ensure a balance of treatment allocations across the study. There are no stratification factors in this study. The IRT system will be utilized to implement the outcome of the disease activity assessments at the appropriate visits.

The randomization scheme will be generated and maintained by the Sponsor. Once all study data have been verified, validated, and the database locked, individual subjects will be unmasked to their treatment. In the event of a medical emergency during the study where the knowledge of subject treatment is required, an individual Principal Investigator will have the ability to unmask the treatment assignment for a specific subject. The Investigator should

notify the Sponsor prior to unmasking a subject, if there is sufficient time. Further, the Sponsor must be informed whenever the randomization code is broken and the reasons for unmasking.

10 STUDY PROCEDURES

10.1 Outline of Study

This is a prospective, randomized, double masked, multicenter, two arm study. Subjects with untreated active CNV secondary to AMD who meet all inclusion/exclusion criteria will be included in the study. The study will be conducted at approximately 200 sites and will randomize approximately 660 subjects.

The Investigator or a designee is responsible for scheduling study visits and ensuring subject compliance with the visit schedule. Subjects missing a scheduled visit should be contacted immediately to reschedule the examination, preferably within the specified study visit period.

SD-OCT imaging, fluorescein angiography (FA) and color fundus photography will be performed at the Screening Visit and the images will be assessed by CRC. The CRC will review these images to confirm subject eligibility based upon the lesion attributes specified in the inclusion/exclusion criteria. Subjects who meet all inclusion and no exclusion criteria and are confirmed as eligible by the CRC will return to the site for the Visit 1/Baseline (Day 0).

At Visit 1/Baseline Visit, subjects will be randomized to one of two arms in a 1:1 ratio.

In Arm 1 (RTH258 6 mg):

RTH258 6 mg will be initially injected 3 times at 4 week intervals, at Visit 1/Day 0, Visit 2/Week 4 and Visit 3/Week 8.

Following the loading doses, each subject will be injected q12 up to Visit24/Week 92 unless there is disease activity assessed according to the guidance provided at Visit 5/Week 16, Visit 6/Week 20, Visit 8/Week 28, Visit 9/Week 32, Visit 11/Week 40, Visit 12/Week 44, Visit 14/Week 52, Visit 15/Week 56, Visit 17/Week 64, Visit 18/Week 68, Visit 20/Week 76, Visit 21/Week 80 or Visit 23/Week 88. If disease activity is identified, the subject will be reassigned to receive injections q8 thereafter, up to study exit. The IRT system will make the necessary changes to the dosing per the masked Investigator’s assessment. The disease activity assessment will also be performed at visit 24/Week 92 but will not be entered into IRT and will have no effect on the subject’s treatment regimen.

Disease Activity Criteria at Week 16:

- Decrease in BCVA of ≥ 5 letters compared with Baseline
- Decrease in BCVA of ≥ 3 letters and CSFT increase ≥ 75µm compared with Week 12
- Decrease in BCVA of ≥ 5 letters due to neovascular AMD disease activity compared with Week 12
- New or worse IRC/IRF compared with Week 12

Disease Activity Criterion at Weeks 20, 28, 32, 40 and 44:

- Decrease in BCVA of ≥ 5 letters due to neovascular AMD disease activity compared with Week 12

Disease Activity Criterion at Weeks 52, 56, 64, 68, 76, 80, 88 and 92:

- Decrease in BCVA of ≥ 5 letters due to neovascular AMD disease activity compared with Week 48

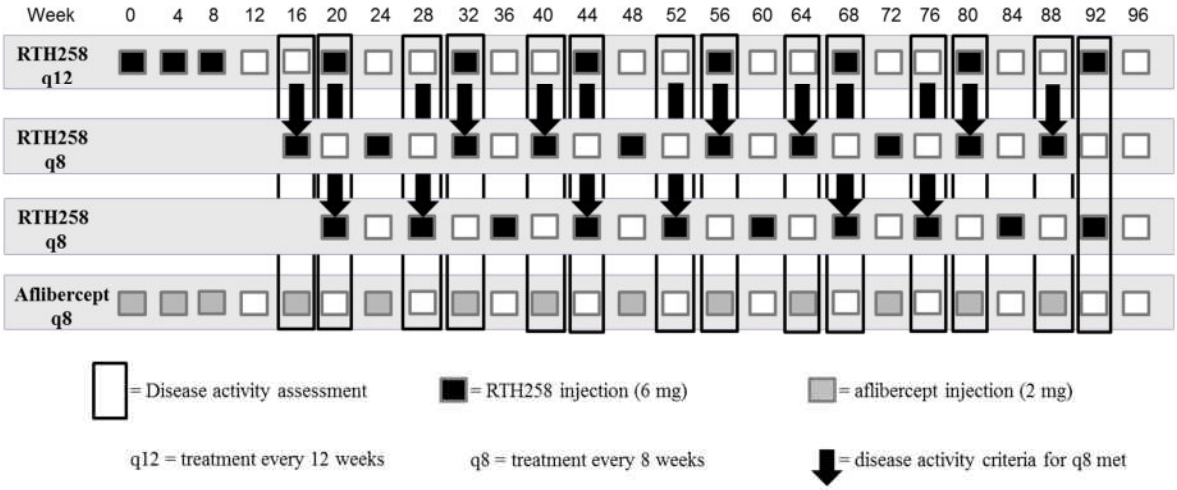
A subject randomized to RTH258 6 mg who misses Visit 5/Week 16, Visit8/Week 28, Visit 11/Week 40, Visit14/Week 52, Visit 17/Week 64, Visit 20/Week 76 and/or Visit 23/Week 88 will undergo the disease activity assessment at the next scheduled visit as he/she would have done if the visit had not been missed. If, however, a subject randomized to RTH258 6 mg misses any of the following disease activity assessment visits (Visit 6/Week 20, Visit 9/Week 32, Visit 12/Week 44, Visit 15/Week 56, Visit 18/Week 68 or Visit 21/Week 80) then the subject will be assumed to have met the disease activity criterion at the missed visit and will be reassigned to a q8 regimen up to study exit. The IRT system will make the necessary changes once the missed visit is registered.

If a subject misses Visit 4/Week 12, then the Visit 3/Week 8 values will be applied as the reference for disease activity assessments up to and including Visit 12/Week 44. If a subject misses Visit 13/Week 48, then the Visit 12/Week 44 values will be applied as the reference for disease activity assessments in the second year of the study.

In Arm 2 (aflibercept 2 mg):

Aflibercept 2 mg, (EYLEA, comparator) treatment is initiated with injections at 4 week intervals (Visit 1/Day 0, Visit 2/Week 4 and Visit 3/Week 8), followed by injections q8 thereafter (Figure 10.1.-1).

Figure 10.1.-1
Dosing schedule by treatment



10.2 Visits and Examinations

Details of all procedures, definitions and grading criteria for test parameters can be found in the Manual of Procedures (MOP) for this protocol.

10.2.1 Screening Visit (Day -14 to Day -2)

The completion of assessments for this visit may occur on different days. The screening period starts with the signing of the ICF.

One time rescreening of subjects will be allowed in the following circumstances: a) laboratory test(s) need to be repeated, b) when a subject has a temporary medical condition precluding participation. As long as testing can be repeated within 14 days of the first screening, the other screening assessments do not need to be repeated. If rescreening is to occur beyond 14 days from the original screening visit date, then all screening procedures must be repeated. Rescreening will not be permitted for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the subject. Medical judgment should be exercised to ensure that treatment is not withheld in order for a subject to participate in the study.

1 Explain the purpose and nature of the study, and have the subject or legally authorized representative read, sign, and date the IRB/IEC-approved ICF (including the optional pharmacogenetics consent, if applicable). Additionally, have the individual obtaining ICF the subject and a witness, if applicable, sign and date the ICF. Provide a copy of the signed document to the subject (or additional original signed document where required) and maintain an original signed document at the site. The ICF must be signed/dated prior to performing study procedures including screening.

2 Obtain demographic information and medical history, including information on all medications used within the past 90 days.

3 Perform a general physical exam.

4 Collect vital signs (blood pressure and pulse).

5 Perform a pregnancy test if the subject is female and of childbearing potential.

6 Obtain blood and urine samples for blood chemistry/hematology and urinalysis and submit the samples to the central laboratory Sample collection should be performed prior to injection of the fluorescein dye.

7 Perform BCVA on both eyes.

8 Perform a complete ophthalmic examination on both eyes including slit-lamp exam, intraocular pressure (IOP) measurement and fundus exam (dilation to be performed at the discretion of the Investigator).

9 Perform SD-OCT on both eyes. Submit the images (within 24 hours, if possible) to the CRC for determination of eligibility.

10 Perform FA on both eyes. Submit the images (within 24 hours, if possible) to the CRC for determination of eligibility.

11 Perform 3-field color fundus photography on both eyes. Submit the images (within 24 hours, if possible) to the CRC for determination of eligibility.

12 Register the subject (including screen fails) in the electronic data capture (EDC) system and obtain a subject ID number.

13 Contact IRT to enter the subject ID number.

14 Monitor for AEs.

15 Schedule Visit 1/Baseline (Day 0) to take place 2 to 14 days after the start of the Screening assessments.

10.2.2 Visit 1/Baseline (Day 0)

At the Baseline Visit, subjects will be randomized only if the subject has successfully met all of the eligibility criteria.

1. Obtain information on any changes in medical health and/or the use of concomitant medications.

2. Record any AEs that are observed or reported, including those associated with changes in concomitant medication dosing.

3. Administer the VFQ-25, using validated translations as applicable and available. The VFQ-25 should be administered prior to any examination.

4. Collect vital signs (blood pressure and pulse).

5. Obtain a blood sample for anti-drug antibody (ADA) analysis. *Blood draws should take place prior to the injection.*

6. Obtain a blood sample for systemic RTH258 analysis. *Blood draws should take place prior to the injection.*

7. Obtain a blood sample for genetic analysis (optional). *Blood draws should take place prior to the injection.*

8. Perform BCVA on both eyes. Baseline BCVA of the study eye must be between 78 and 23 letters, inclusive, for the subject to qualify.

9. Perform a complete ophthalmic examination on the study eye including slit-lamp exam, IOP measurement, and fundus exam (dilation to be performed at the discretion of the Investigator).

10. Perform SD-OCT imaging on study eye and submit the images to the CRC.

11. Where applicable, perform fundus autofluorescence (FAF) imaging on the study eye and submit the images to the CRC. FAF will only be performed at a subset of sites. Dilation to be performed at the discretion of the Investigator.

12. Verify that all eligibility criteria have been met, including the required screening imaging eligibility from the CRC. The Investigator should also review the results from the central laboratory for the samples collected at Screening to determine if there is anything that would preclude participation of the subject.

13. Contact IRT to obtain a kit number.

14. Have the unmasked Investigator perform an IVT injection according to the randomization/kit assignment. The injection procedure may be performed at a later time, as long as it is within 7 days of the scheduled visit.

15. After the injection, perform a postinjection assessment of the study eye 0-5 minutes and 30 (± 15) minutes after injection (and at further time points, as needed).

16. Schedule Visit 2/Week 4 to take place 28 ± 3 days after the Visit 1/Baseline.

10.2.3 Visit 2/Week 4 (Day 28 ± 3 days) and Visit 3/Week 8 (Day 56 ± 3 days)

1. Obtain information on any changes in medical health and/or the use of concomitant medications.

2. Record any AEs that are observed or reported, including those associated with changes in concomitant medication dosing.

3. Collect vital signs (blood pressure and pulse).

4. Perform BCVA on the study eye.

5. Perform a complete ophthalmic examination on the study eye including slit-lamp exam, IOP measurement, and fundus exam (dilation to be performed at the discretion of the Investigator).

6. Perform SD-OCT imaging on study eye and submit the images to the CRC.

7. Contact IRT and obtain a kit number.

8. Have the unmasked Investigator perform an IVT injection according to the randomization/kit assignment. The injection procedure may be performed at a later time, as long as it is within 7 days of the scheduled visit and within the visit window.

9. After the injection, perform a postinjection assessment of the study eye 0-5 minutes and 30 (± 15) minutes after injection (and at further time points, as needed).

10. Schedule Visit 4/Week 12 to take place 84 ± 7 days after the Visit 1/Baseline.

10.2.4 10.2.4 Visit 4/Week 12 (Day 84 ± 7 days) through Visit 24/Week 92 (Day 644 ± 7 days)

1. Obtain information on any changes in medical health and/or the use of concomitant medications.

2. Record any AEs that are observed or reported, including those associated with changes in concomitant medication dosing.

3. Administer the VFQ-25 using validated translations as applicable and available (*Visit 7, Visit 13 and Visit 19 only*).

4. Perform a general physical exam (*Visit13 only*).

5. Collect vital signs (blood pressure and pulse).

6. Perform a pregnancy test if the subject is female and of childbearing potential (*Visit 13 only*).

7. Obtain blood and urine samples for blood chemistry/hematology and urinalysis and submit the samples to the central laboratory (*Visit 4 and Visit 13 only*). *Sample collection should be performed prior to any IVT or sham injection and prior to injection of fluorescein dye.*

8. Obtain a blood sample for anti-drug antibody (ADA) analysis (*Visit 4, Visit 7, Visit 10, Visit 13, Visit 18, Visit 23 only*). Blood draws should be performed prior to any IVT or sham injection and prior to injection of fluorescein dye.

9. Obtain a blood sample for systemic RTH258 analysis (*Visit 4, Visit 7, Visit 10, Visit 13, Visit 18, Visit 23 only*). Blood draws should be performed prior to any IVT or sham injection and prior to injection of fluorescein dye.

10. Perform BCVA on the study eye. Perform BCVA on both eyes (*Visit 4, Visit 7, Visit 10, Visit 13, Visit 16, Visit 19 and Visit 22 only*).

11. Perform a complete ophthalmic examination on the study eye including slit-lamp exam, IOP measurement and fundus exam (dilation to be performed at the discretion of the Investigator). Perform a complete ophthalmic exam on both eyes (*Visit 13 only*).

12. Perform SD-OCT imaging on study eye and submit the images to the CRC. Perform SD-OCT on both eyes and submit the images to the CRC (*Visit 13 only*).

13. Perform FA on both eyes (*study eye at Visit 4 and both eyes at Visit 13*) and submit the images to the CRC (Visit 4 and Visit 13 only).

14. Perform color fundus photography (*on study eye at Visit 4*) and submit the images to the CRC (*Visit 4 and Visit 13*).

15. Where applicable, perform FAF imaging on the study eye and submit the images to the CRC (*Visit 4 and Visit 13 only*). FAF will be performed at a subset of sites.

16. Have the masked Investigator perform the visit appropriate disease activity assessment for the study eye (*Visit 5, Visit 6, Visit 8, Visit 9, Visit 11, Visit 12, Visit 14, Visit 15, Visit 17, Visit 18, Visit 20, Visit 21, Visit 23 and Visit 24*).

17. Contact IRT (*all visits except Visit 4*).

18. Have the unmasked Investigator perform an IVT or sham injection according to the randomization/kit assignment (*except Visit 4*). The injection procedure may be performed at a later time, as long as it is within 7 days of the scheduled visit and within the visit window.

19. After the injection, perform a postinjection assessment of the study eye 0-5 minutes and 30 (± 15) minutes after injection/sham (*except Visit 4*) (and at further timepoints, as needed).

20. Schedule Visits 5 through 24 as appropriate per visit window. Schedule Visit 25/Week 96 to take place 672 ± 7 days after Visit 1/Baseline

10.2.5 Visit 25/Week 96/Exit Visit (Day 672 ± 7 days) or Early Exit

1. Obtain information on any changes in medical health and/or the use of concomitant medications.

2. Record any AEs that are observed or reported, including those associated with changes in concomitant medication dosing.

3. Administer the VFQ-25 using validated translations as applicable and available. The VFQ-25 should be administered prior to any examination.

4. Perform a general physical exam.

5. Collect vital signs (blood pressure and pulse)

6. Perform a pregnancy test if the subject is female and of childbearing potential

7. Obtain blood and urine samples for blood chemistry/hematology and urinalysis and submit the samples to the central laboratory. Blood draws should be performed prior to injection of fluorescein dye.

8. Obtain a sample for ADA analysis (if the subject exits at or before Visit 23/Week 88). Blood draws should be performed prior to injection of fluorescein dye.

9. Obtain a sample for systemic RTH analysis (if the subject exits at or before Visit 23/Week 88). Blood draws should be performed prior to injection of fluorescein dye.

10. Perform BCVA on both eyes.

11. Perform a complete ophthalmic examination on both eyes including slit-lamp exam, IOP measurement and fundus exam (dilation to be performed at the discretion of the Investigator).

12. Perform SD-OCT imaging on the both eyes and submit the images to the CRC.

13. Perform FA on both eyes and submit the images to the CRC.

14. Perform color fundus photography on both eyes and submit images to the CRC

15. Where applicable, perform FAF on the study eye and submit the images to the CRC. FAF will only be performed at a subset of sites.

16. Complete the Exit Form.

10.3 Unscheduled Visits

If a subject returns to the site prior to his/her next scheduled study visit for assessment of an adverse event (eg, follow up on elevated IOP for the study eye), the Unscheduled Visit pages of the electronic case report form (CRF) should be completed. Procedures conducted at the Unscheduled Visit are at the discretion of the Investigator apart from treatments of the study eye for AMD. If the subject is discontinuing from the study at the Unscheduled Visit, the CRFs for the Exit Visit should be completed rather than the CRFs for an Unscheduled Visit. Routine treatments and routine follow up of the nonstudy eye will not be considered an Unscheduled Visit. Any treatments of the nonstudy eye will be captured on the Concomitant Medication Page.

10.4 Discontinued Subjects

Discontinued subjects are those who are lost to follow up, withdraw or are withdrawn from the study after the Visit 1/Baseline. Subjects may discontinue from the study at any time for any reason. Discontinued subjects will not be replaced (ie, their subject numbers will not be re-assigned/re-used). The site must contact IRT to register the subject's discontinuation from IP.

Should a subject exhibit any clinically relevant signs, symptoms, or other clinical observations that possibly could be associated with suspected sensitivity or intolerance to one of the study treatments, the Investigator must document those observations on an AE Form (AEF). If a subject discontinues the study with an ongoing AE, follow up procedures, as appropriate and outlined in Section 12.6, should be performed.

Any subject who exits early from the study must undergo all procedures outlined at Visit 25/Week 96 (Section 10.2.5). Additionally, the Exit Form must be completed and a reason for discontinuation must be identified.

If a subject exits early from the study between visits, the Investigator must attempt to contact the subject and request the subject to return for a final visit to complete the exit procedures. If the subject is unable or unwilling to return for the Exit Visit, the subject will be considered lost to follow up and the 'date of exit' will be the date that the subject was last seen at the site or contacted by other communication.

Finally, to ensure the safety of all subjects who exit early from the study, Investigators should assess each subject and, if necessary, advise them of any therapies and/or medical procedures that might be needed to maintain their health.

10.5 Discontinuation of Study Treatment

The Investigator may discontinue study treatment for a given subject and/or withdraw the subject from study if he/she believes that continuation would pose a risk to their health. Subjects can be discontinued from study treatment because of

- appearance of a new health condition suspected to require appropriate care or require medications prohibited by the protocol
- refusal to continue treatment, or at the Investigator's discretion based on his/her clinical judgement the subject requires rescue medication
- use of prohibited treatment during the study
- investigator's discretion based on his/her clinical judgment
- positive urine/serum pregnancy test

Subjects who discontinue study treatment should NOT be considered withdrawn from the study. Subjects are expected to continue with the study visits and procedures as long as such procedures do not pose a risk to the well being of the subject. Site personnel must also contact IRT to register the subject's discontinuation from study treatment.

The appropriate personnel from the site and Sponsor will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

10.6 Clinical Study Termination

If the clinical study is prematurely terminated or suspended, the Sponsor will inform the Investigator and the regulatory authorities of the termination/ suspension and the reason(s) for the termination/suspension. The Investigator should promptly notify the IEC/IRB of the termination or suspension and of the reasons. The Sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time, for reasonable cause.

Reasons for the closure of an investigational site or termination of a study may include:

- The Investigator fails to comply with the protocol or GCP guidelines
- Safety concerns
- Sufficient data suggesting lack of efficacy
- Inadequate recruitment of subjects by the Investigator

The Investigator also may terminate the study at his/her site for reasonable cause. If the Sponsor terminates the study for safety reasons, it will immediately notify the Investigator(s) by telephone and subsequently will provide written confirmation of and instructions for study termination. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the IRBs/IECs of the early termination of the trial.

10.7 Study Methods and Measurements

10.7.1 Visual Function Questionnaire-25

Quality of life data will be collected with a visual function questionnaire using the National Eye Institute VFQ-25 which is a validated instrument that has been used in many studies of subjects with AMD. The VFQ-25 will be administered by masked site staff to subjects at sites where local language versions are available, validated, and approved by the IEC/IRB. The VFQ-25 must be administered before any other examination. The United States English version of the VFQ-25 is included in the MOP.

10.7.2 General Physical Exam and Vital Signs

The physical exam will consist of a routine evaluation of organ systems, eg, ears, eyes, nose, throat, neck, lymph nodes, lungs, heart, abdomen, skin/extremities, neurological, and musculoskeletal systems. After Screening, the physical exam will also include a discussion with the subject if there have been changes in his/her physical condition since the Screening

exam. All clinically significant findings will be recorded as medical history or adverse events, as appropriate.

Vital signs consist of blood pressure and pulse rate measurements. Standardized procedures for each are provided in the MOP.

10.7.3 Pregnancy Tests

A pregnancy test will be conducted for all women of child bearing potential at Screening, Visit 13/Week 48, and Exit Visit. Urine pregnancy tests will be performed unless local regulations require serum pregnancy tests. Additional pregnancy testing may be conducted at the Investigator's discretion or if required by local regulations.

10.7.4 Laboratory Analysis of Blood and Urine

Blood and urine samples will be shipped to a central laboratory. Results of the analysis will be provided to the Investigator who will assess those from Screening prior to randomizing the subject to determine if there is anything that would preclude participation of the subject and at subsequent visits to assess any changes from Screening. A standardized procedure for the collection and processing of blood and urine is provided by the central laboratory. A list of laboratory parameters is provided in the MOP. If a subject should present with a clinically significant change resulting in an adverse event, as assessed by the Investigator, a decision will be made as to subject continuation in the trial. This decision will take into account the adverse event characteristics including but not limited to seriousness and relationship to study drug.

10.7.5 Analysis of Anti-Drug Antibodies (ADA) and Systemic RTH258

Collection of blood for ADA and systemic RTH258 will occur at the study site. Blood draws should take place prior to the injection/sham. A standardized procedure for the collection, processing, storage and shipment of these blood samples is provided by the central laboratory.

[redacted]

10.7.7 Best-Corrected Visual Acuity

ETDRS visual acuity testing should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye. Visual acuity testing should be done following refraction and completed according to the procedure outlined in the MOP. Certification of the equipment and examiners at each investigative site will occur prior to any evaluation of study subjects.

Subjects in some countries will undergo BCVA testing using numerical charts rather than letter charts.

10.7.8 Complete Ophthalmic Examination

A complete description of standardized procedures and grading scales is outlined in the MOP. The ophthalmic exam will consist of the following:

- Slit-lamp examination – includes evaluation of the lids/lashes, conjunctiva, cornea, anterior chamber aqueous reaction (cell and flare), iris, lens and anterior part of the vitreous body.
- IOP measurement – a measurement of the intraocular pressure will be conducted using an applanation tonometer or Tonopen. The same method should be used throughout the study for each subject.
- Fundus Exam – includes evaluation of the vitreous, retina, macula, choroid, and optic nerve. Dilation for the fundus exam is at the discretion of the Investigator.

10.7.9 Spectral Domain Optical Coherence Tomography Imaging

A standardized procedure for the collection of quantitative and qualitative data via SD-OCT is provided by the CRC in a separate hand book. Each site must select a single brand of equipment for use on all subjects at that site. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects. At the Screening Visit, SD-OCT images will be submitted to the CRC for determination of eligibility. Feedback from the CRC following expedited review will be provided to the sites via email or fax. The CRC may participate in assessment of new disease activity, as appropriate.

10.7.10 Fluorescein Angiography

A standardized procedure for the collection of FA images is provided by the CRC in a separate hand book. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects. At the Screening Visit, retinal images will be submitted to the CRC for determination of eligibility. FA images from previous routine evaluations may be used for the screening FA as long as they were performed within 3 days of the Screening Visit using CRC-certified equipment and examiners. Feedback from the CRC following expedited review will be provided to the sites via email or fax.

10.7.11 Color Fundus Photography

A standardized procedure for the collection of 3-field color fundus photographic images is provided by the CRC in a separate hand book. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects. At the Screening Visit retinal images will be sent to the CRC for determination of eligibility. Feedback from the CRC following expedited review will be provided to the sites via email or fax.

10.7.12 Fundus Autofluorescence

FAF will be performed at a subset of sites in order to assess the occurrence of geographic atrophy. A standardized procedure for the collection of FAF images is provided by the CRC in a separate hand book. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects. FAF will not be used to determine eligibility, but will be included beginning at the Visit 1/Baseline.

10.7.13 Disease Activity Assessment

The masked Investigator will assess the study eye of all subjects at Visit 5/Week 16, Visit 6/Week 20, Visit 8/Week 28, Visit 9/Week 32, Visit 11/Week 40, Visit 12/Week 44, Visit 14/Week 52, Visit 15/Week 56, Visit 17/Week 64, Visit 18/Week 68, Visit 20/Week 76, Visit 21/Week 80 and Visit 23/Week 88. The IRT system will make the necessary changes to the dosing per the masked Investigator's assessment. The disease activity assessment will also be performed at Visit 24/Week 92, but will not be entered into IRT, and will have no effect on the subject's treatment regimen. Details of the disease activity assessments are further outlined in the MOP.

10.7.14 Intravitreal Administration of Investigational Product

The IVT injection procedure for both the test article and control article is the same as that described for aflibercept in the product information sheet. IVT injection is contraindicated in subjects with active ocular or periocular infections and in subjects with active intraocular inflammation; therefore, the Investigator should verify that these conditions are not present in either eye (study and nonstudy eyes) prior to every injection. Specific instructions for injection procedures are provided in the MOP.

10.7.15 Administration of Sham Injection

Beginning at Week 12, at visits when subjects do not receive an active injection they will be administered a sham injection. For the sham injection the tip of an injection syringe (the hub without needles) will be used. A standardized procedure for the sham is described in the MOP.

10.7.16 Postinjection Assessment

The study eye will be assessed before, immediately (0-5 minutes) after and 30 (± 15) minutes after each IVT/sham injection to ensure that the procedure and/or the study medication have not endangered the health of the eye. The postinjection assessments include an evaluation of the central retinal artery perfusion via a gross assessment of vision (e.g., count fingers) and

measurement of IOP according to the schedule detailed in the MOP. Direct visualization to assess the central retinal artery, presence of retinal detachment, presence of new intraocular hemorrhage(s) might be appropriate at the discretion of the investigator and/or based on the results of gross assessment of vision and IOP measurement. **Assessments will continue until the central retinal artery is adequately perfused and the IOP is within 10 mmHg of the pre-injection value and is stable in the opinion of the Investigator.** Any subject who develops significantly raised IOP (> 30 mmHg) or a non-adequately perfused central retinal artery at any time during the study should be monitored according to the Investigator's clinical judgment and may undergo additional procedures and measurements of IOP beyond those specified in the protocol. If, at the conclusion of the required evaluation period following an injection/sham, there are no safety concerns, the subject will leave the site. If any concern or immediate toxicity is noted, the subject will remain at the site and will be treated according to the designated evaluating physician's clinical judgment. If any issues regarding IOP were noted during the postinjection assessment, then the subject should be scheduled for a follow up visit (Unscheduled Visit) the day following injection/sham, if required in the opinion of the Investigator. Clinically relevant changes that are observed during the postinjection assessment should be reported as adverse events.

10.8 Concomitant Treatment

The Investigator should instruct the subject to notify the study site about any new medications he/she takes after enrolling into the study.

Should the nonstudy eye require treatment during the study with an anti-VEGF, a drug which is approved for the treatment of neovascular AMD in the respective country should be applied at the discretion of the Investigator and following the procedures established at the respective site. The nonstudy eye treatment may occur at any time once the Baseline study injection has been administered.

10.9 Prohibited Treatment

Use of treatments, as displayed in Table 10.9.-1. are not allowed after the start of the study i.e., Screening. In addition, there are certain washout periods to be respected as outlined in the exclusion criteria.

Table 10.9.-1.
Prohibited Treatment

Medication
Study eye: Intra- or periocular corticosteroids
Study eye: Laser treatment for AMD
Study eye: Anti-VEGF therapy other than IP
Nonstudy eye: Unapproved or Investigational treatment
Systemic: Use of systemic corticosteroids for 30 or more consecutive days (except low stable doses of corticosteroids [defined as ≤10 mg prednisolone or equivalent dose], inhaled, nasal or dermal steroids are permitted)
Systemic: Anti-VEGF therapy
Any investigational drug, biologic or device (with the exception of over-the –counter vitamins, supplements or diets)

11 ANALYSIS PLAN

11.1 General considerations

Continuous variables will be summarized for the measured values and change from Baseline values using the number of observations, mean, standard deviation, median, quartiles, minimum and maximum. Categorical variables will be summarized with numbers and percent from each category. Treatment differences will be presented together with 95% confidence intervals as appropriate.

11.2 Subject Evaluability

Subject evaluability based on pre-specified deviations and their impact on analysis sets will be determined prior to breaking the masked treatment assignment code and locking the database for the primary analysis at Week 48. Protocol deviations and their impact on analysis sets will be pre-specified in the deviations and evaluability plan (DEP).

11.3 Analysis Data Sets

The following analysis sets are defined:

All enrolled analysis set: includes all subjects who signed an ICF and are assigned subject numbers. This analysis set will be used to summarize subject disposition and pre-treatment adverse events.

All randomized analysis set: includes all subjects who were randomized. This analysis set will be used to describe the randomized study population based on demographics and baseline characteristics.

Safety analysis set: includes all subjects who received at least one IVT injection. Subjects in the safety analysis set will be analyzed according to the first treatment received. This analysis set will be used for all safety analyses.

Full analysis set (FAS): includes all subjects who are randomized and received at least one IVT injection. Following the intent-to-treat (ITT) principle, subjects in the FAS will be analyzed according to the treatment group they are assigned at randomization. The FAS will be the primary analysis set for efficacy analyses.

The per protocol analysis set (PPS): defined for the primary and key secondary efficacy analysis at Week 48 includes all subjects in the FAS with no protocol deviations that are expected to majorly affect the assessment of efficacy at Week 48 including: lack of

compliance (including treatment misallocation), missing data, concomitant medication and deviation from inclusion/exclusion criteria. Discontinuation from treatment due to lack of efficacy does not constitute a reason for exclusion from the PPS.

Before the Week 48 database lock the relevant protocol deviations will be specified in the deviations and evaluability plan (DEP) document and identified at the subject level in the database.

11.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for all analysis sets. All summaries will be presented by treatment group and overall.

11.4.1 Demographic Characteristics

The demographic parameters are age category (50 to 64, 65 to 74, 75 to 84, and ≥ 85), gender, ethnicity and race. Age will also be summarized as a continuous variable.

11.4.2 Baseline Characteristics

Baseline characteristics will include: primary diagnosis of neovascular AMD, time since diagnosis of neovascular AMD (days), whether neovascular AMD is unilateral or bilateral, BCVA (both as a continuous variable and using categories (≤ 55, 56-70, ≥ 71 letters), lesion type (predominantly classic, minimally classic, occult), foveal involvement (subfoveal, extrafoveal, undeterminable), CNV lesion size, presence of sub retinal fluid, presence of intraretinal fluid/cyst, presence of sub RPE fluid, neurosensory retinal thickness and central subfield thickness (CSFT) (both as a continuous variable and using categories (< 400, ≥ 400 µm).

11.5 Primary and Key Secondary Efficacy Analyses

Primary Efficacy Endpoint:

- Change in BCVA from Baseline to Week 48

Key Secondary efficacy Endpoints:

- 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.
- q12 treatment status at Week 48 for subjects randomized to RTH258 6 mg.

- q12 treatment status at Week 48 within the subjects randomized to RTH258 6 mg, with no q8 need during the 1st q12 cycle (Week 16 and Week 20).

The primary and first key secondary endpoints will be analyzed based on the FAS with last-observation-carried-forward (LOCF) imputation of missing BCVA values (primary and first key secondary endpoint) and a negative q12 treatment status at Week 48 in the case of incomplete active treatment up to Week 48 (second and third key secondary endpoint). The analysis of the primary and key secondary endpoints based on the PPS will be considered supportive. 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 data sets.

11.5.1.1 Statistical Hypotheses

The statistical hypothesis for the primary endpoint and first key secondary endpoint is to demonstrate non-inferiority of RTH258 6 mg to aflibercept 2 mg within a margin of 4 letters.

The following 2 hypotheses will be tested in the pre-specified hierarchical sequence according to their numbering (HAn, n=1,2). Consequently, confirmatory testing of the second hypothesis requires rejection of the first null hypothesis. In this setting, each hypothesis will be assessed at a two-sided significance level of 0.05, while keeping the global type I error rate at 0.05.

Hypotheses: The following noninferiority hypotheses are related to a noninferiority margin of 4 letters.

$_{48}$ = Week 48, $_{36\text{-}48}$ = Week 36 through 48, $_{R6}$=RTH258 6mg, $_{A}$= aflibercept 2 mg

$\mathbf{H_{01}}$: $\mu_{48R6} - \mu_{48A} \leq$ -4 letters vs $\mathbf{H_{A1}}$: $\mu_{48R6} - \mu_{48A} >$ -4 letters

μ_{48R6} and μ_{48A} being the corresponding unknown true mean BCVA changes from Baseline to Week 48.

$\mathbf{H_{02}}$: $\mu_{36\text{-}48R6} - \mu_{36\text{-}48A} \leq$ -4 letters vs $\mathbf{H_{A2}}$: $\mu_{36\text{-}48R6} - \mu_{36\text{-}48A} >$ -4 letters

$\mu 36\text{-}48_{R6}$ and $\mu 36\text{-}48_{A}$ being the corresponding unknown true mean values for the average change in BCVA from Baseline over the period Week 36 through 48.

11.5.2 Statistical Methods

For the test of non-inferiority, a two-sided 95% confidence interval for the treatment difference will be derived from an analysis of variance (ANOVA) model with treatment,

baseline BCVA categories (≤ 55, 56-70, ≥ 71 letters) and age categories (< 75, ≥ 75 years) as fixed effects. In order to demonstrate noninferiority, the lower limit of the two-sided 95% confidence interval for the treatment difference (RTH258 6 mg – aflibercept 2 mg) must be greater than -4 letters representing the noninferiority margin.

The q12 treatment status of subjects in the RTH258 6 mg treatment arm will be presented descriptively together with exact 95% confidence intervals for the proportion of subjects with a positive status.

- For the overall proportion of subjects with a positive q12 treatment status at week 48, the denominator is all FAS subjects in the RTH258 6 mg group, and the numerator is the corresponding number of subjects with no identified need for treatment at q8 at Week 16, 20, 28, 32, 40 and 44 (while missing Week 16, Week 28 and/or Week 40 assessment is considered as no q8 treatment needed)
- For the predictability of the adequacy of q12 treatment, based on the absence of disease activity during the first q12 cycle, the denominator is all FAS subjects in the RTH258 6 mg group with no identified need for treatment q8 at Week 16 and Week 20 (while missing Week 16 assessment is considered as no q8 treatment needed), and the numerator is the corresponding number of subjects with a positive q12 treatment status at Week 48, i.e., with no identified need for treatment at q8 at Week 16, 20, 28, 32, 40 and 44 (while missing Week 16, Week 28 and/or Week 40 assessment is considered as no q8 treatment needed)

11.5.3 Sensitivity Analysis

Sensitivity analysis to explore the robustness of the primary and first key secondary efficacy results with respect to protocol deviations will use the PPS with LOCF imputation of missing values using the same model and factors as in the primary efficacy analysis model.

Sensitivity analyses to explore the robustness of the primary and first key secondary efficacy analysis results related to missing values will be performed on the observed data in the FAS applying the specified ANOVA model, and a mixed model repeated measures (MMRM).

11.5.4 Subgroups

The following subgroups will be analyzed for the primary and key secondary efficacy endpoints:

- Age category (< 75 years and ≥75 years)
- Gender (male and female)

- Baseline BCVA categories (≤ 55, 56-70, ≥ 71 letters)
- Baseline CSFT category (< 400, ≥ 400)
- Baseline lesion type (predominantly classic, minimally classic, occult)
- Baseline lesion size (tertiles) by lesion type (predominantly classic vs minimally classic/occult

11.6 Additional Secondary Efficacy Analyses

The following secondary efficacy endpoints will be analyzed primarily based on the FAS:

- 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
- 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 6 mg only)
- q12 treatment status at Week 96 within the subjects with no q8-need during the 1st q12 cycle (ie, at Week 16 and Week 20) (for subjects randomized to RTH258 6 mg only)
- Change in CSFT from Baseline to each postbaseline visit
- Change in neurosensory retinal thickness from Baseline to each postbaseline visit
- Change in CNV lesion size from Baseline to Weeks 12, 48 and 96
- Absence of subretinal fluid at each visit
- Absence of intraretinal fluid at each visit
- q8 treatment need status assessed at Weeks 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88 and 92
- Change in patient reported outcomes (VFQ-25) total and subscale scores from Baseline to Weeks 24, 48, 72 and 96

Statistical methods for the analysis of each of the secondary endpoints will be described in the statistical analysis plan (SAP).

11.7 Handling of Missing Data

The primary presentation of efficacy results will use LOCF for the imputation of missing values supplemented by presentations on the observed data only.

All non-missing postbaseline values including assessments conducted at unscheduled visits will be used when implementing the LOCF imputation.

Imputation related to the evaluation of the q12 treatment status at week 96 will follow the concept described for Week 48.

11.8 Multiplicity

No alpha adjustment will be applied for testing the hypotheses for the primary and first key secondary efficacy analyses as the two hypotheses will be tested in the pre-specified hierarchical sequence according to their numbering. Consequently, confirmatory testing of the second hypothesis requires rejection of the first null hypotheses. In this setting each hypothesis will be assessed at a two-sided $\alpha = 0.05$, while keeping also the global type I error rate at 0.05. Other key secondary endpoints are not associated with hypothesis testing.

11.9 Safety

11.9.1 Treatment exposure

The extent of treatment exposure will be presented based upon the overall number of injections, the number of subjects injected per visit, and frequency of the different treatment patterns.

11.9.2 Medical History

Relevant medical history (ocular and nonocular) will be tabulated by system organ class and preferred term of the MedDRA dictionary. Ocular events will be presented by study and non-study eye.

11.9.3 Concomitant Therapies

The number and percentage of subjects taking concomitant therapies will be summarized by preferred term according to the WHO Drug Reference List dictionary. Ocular therapies will be presented by study and nonstudy eye.

11.9.4 Safety parameters

The following safety parameters will be descriptively analyzed to assess treatment emergent changes or changes specifically related to the injection procedure using postinjection assessments:

- Adverse events
- General physical exam
- Vital signs
- Laboratory tests (blood chemistry, hematology and urinalysis)
- Worsening in BCVA
- Slit-lamp examination
- Fundus exam
- IOP
- Postinjection assessment
- ADA levels
- Systemic RTH258 levels

11.9.5 Adverse Events

AEs will be coded using the MedDRA dictionary and presented by system organ class and preferred term. Treatment emergent AEs will be analyzed based on the number and percentage of subjects with at least one AE in the category of interest. Separate presentations will be provided related to ocular events in the study eye and nonstudy eye and non-ocular events. Additional summaries will be provided by severity and causality (separately assessed for the injection procedure and the drug). Serious Adverse Events and adverse events leading to discontinuation of study treatment will also be summarized separately.

Subject listings of all adverse events will be provided. Deaths and other serious or clinically significant non-fatal adverse events will be listed separately.

Events of special interest (ESIs; as defined in section 12.3) will be presented based on their incidences.

11.10 Interim Analyses

The primary efficacy analysis will be based on the Week 48 data. The database, including all Week 48 data, will be locked once all active subjects have completed the Week 48 Visit. Systemic RTH258 and ADA data up to Week 36 will be analyzed for the Week 48 primary analysis. The primary analysis at Week 48 will be performed with an unmasking of specified Novartis/Alcon individuals who are not involved in the direct conduct of the trial.

Subjects will remain in the study and will continue to receive masked treatment through the planned duration (96 Weeks) to allow for further masked evaluation of efficacy and safety. Treatment masking of individual subjects will remain intact for all subjects, Investigators, and Alcon staff who have contact with subjects or Investigators or those who are involved in the direct conduct of the study until the final database lock has occurred.

11.11 Sample Size Justification

A sample size of 297 subjects per treatment arm is sufficient to demonstrate noninferiority (margin = 4 letters) of RTH258 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.

12 ADVERSE EVENTS

12.1 General Information

An AE is any untoward medical occurrence in a subject who is administered a study treatment regardless of whether or not the event has a causal relationship with the treatment. An AE, therefore, can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study treatment, whether or not related to the treatment. In clinical studies, an AE can include any untoward medical occurrence occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The determination of clinical relevance is based upon the medical judgment of the Investigator.

12.2 Monitoring for Adverse Events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking the standard questions:

- "Have you had any health problems since your last study visit?"
- "Have there been any changes in the medicines you take since your last study visit?"

AEs should be reported for any clinically relevant change in concomitant medication(s) that is the result of an untoward (unfavorable and unintended) change in a subject's medical health.

Changes in any protocol-specific parameters and questionnaires (if applicable) evaluated during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter or questionnaire response that is clinically relevant is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

12.3 Procedures for Recording and Reporting AEs and SAEs

Subsequent to signing an ICF, all untoward medical occurrences that occur during the course of the study must be documented on the adverse event CRF. When possible, signs and symptoms indicating a common underlying pathology should be documented as one comprehensive event. For each recorded event, the AE documentation must include the onset date, outcome, resolution date (if event is resolved), intensity (ie, severity), any action with study treatment taken as a result of the event, and an assessment of the adverse event's relationship to the study treatment.

Nonserious Adverse Events

A nonserious AE is defined as any untoward change in a subject's medical health that does not meet serious criteria noted below (eg, is not life-threatening, does not require hospitalization, does not prolong a current hospitalization, is not disabling, etc.). All adverse events must be reported regardless of whether or not they are related to the study treatment.

For nonserious adverse events, details should be entered on the adverse event CRF according to instructions provided by the Sponsor.

Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse experience that meets any of the following criteria:

- Results in death.
- Is life-threatening.
  NOTE: Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  NOTE: In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be

considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

All available information on a serious adverse event(s) and any other associated AE, if applicable, must be forwarded to the Sponsor immediately (ie, within 24 hours of the Investigator's or site's knowledge of the event) as follows:

- **In studies utilizing EDC, all available information for the SAE and any associated AE(s) must be entered immediately into the EDC system.**
  NOTE: *Should the EDC system become non-operational, the site must complete the appropriate Serious Adverse Event Form. The completed form is faxed to the Sponsor at* [redacted] *within 24 hours of the Investigator's or site's awareness; however, the reported information must be entered into the EDC system once it becomes operational.*
- Sponsor representatives and their contact information are provided in the MOP that accompanies this protocol.
- Additional information for any applicable event is to be reported as soon as it becomes available.

In addition to the reporting of SAEs to the Sponsor, the SAE must be reported to the IEC / IRB according to their requirements. In addition, SAEs will be reported to regulatory agencies based upon local reporting requirements.

If the SAE is not previously documented in the Investigator's Brochure and is thought to be related to the investigational treatment the Sponsor may urgently require further information from the investigator for Health Authority reporting. Sponsor may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

If the SAE was due to a hospitalization of the subject, a copy of the discharge summary should be made available to the Sponsor, upon request. In addition, a letter from the Investigator that summarizes the events related to the case as well as results of any relevant

laboratory tests may also be requested. Further, depending upon the nature of the SAE, the Sponsor may request copies of applicable portions of the subject's medical records.

An assessment of seriousness will also be performed for all adverse events by a Sponsor physician utilizing the same criteria. If an adverse event reported for an Investigator's subject is upgraded to a serious adverse event by a Sponsor physician, the Investigator will receive a notification from the Sponsor.

Adverse Events of Special Interest

An adverse event of special interest (ESI) is one of scientific and medical concern specific to the Sponsor's product or program where ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. These adverse events may be serious or nonserious. Applicable adverse events may require further investigation in order to characterize and understand, and depending upon the nature of the event, rapid communication by the Sponsor to other parties may also be required.

These ESIs must be reported using the same mechanism (EDC or fax) and timeframe (ie, within 24 hours of the Investigator's or site's knowledge of the event) as described previously for serious adverse events. The ESIs include 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 postinjection
- Any elevation of IOP requiring surgical intervention (eg, paracentesis)
- New retinal tear or detachment
- New vitreous hemorrhage > 2+ severity that does not resolve within 14 days of the onset of the event (see MOP for grading scale)
- New diagnosis of geographic atrophy
- Arterial thromboembolic events

As with all AEs occurring in a study subject, a decision will be made by the Investigator concerning further exposure to study treatment and further participation in the study.

12.4 Intensity and Causality Assessments

For every AE, the Investigator must assess the intensity (severity) and causality (relationship to study treatment). Specifically, AEs should be classified as mild, moderate, or severe. The assessment of causality will be based upon the categories of related and not related. These classifications should be based on the following definitions:

Intensity (Severity):

Mild	An AE is mild if the subject is aware of, but can easily tolerate the sign or symptom.
Moderate	An AE is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
Severe	An AE is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activity.

Causality:

Related	An AE considered related to the use of the study treatment. AEs classified as related may be either definitely related or possibly related where a direct cause and effect relationship between the study treatment and the AE has not been demonstrated but there is a reasonable possibility that the AE was caused by the study treatment.
Not Related	An AE considered unrelated to the use of the study treatment. AEs classified as not related may either be definitely unrelated or simply unlikely to be related (ie, there are other more likely causes for the AE).

An assessment of causality will also be performed, when appropriate, by a Sponsor physician utilizing the same definitions. For a SAE reported by an Investigator as not related that is subsequently upgraded to be related by a Sponsor physician, the Investigator will receive a notification.

12.5 Unmasking of the Study Treatment

In the case of emergency, information on the identity of the masked assigned IP is available to Investigators. If the treatment code needs to be broken in the interest of the subject safety, the Investigator is encouraged to contact an appropriate unmasked Sponsor representative prior to unmasking if there is sufficient time. Dependent upon the individual circumstances (ie, medical emergency), the code may be broken by contacting the IRT system prior to

contact with the Sponsor. The Sponsor must be informed in all cases in which the code was broken and of the circumstances involved.

Additionally, the Sponsor may be required to unmask the subject if the AE meets criteria of a SUSAR in order to fulfill expedited regulatory reporting requirements.

12.6 Follow-up of Subjects with Adverse Events

The Investigator is responsible for adequate and safe medical care of subjects during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. Any additional data from these follow-up procedures must be documented and available to the Sponsor.

12.7 Pregnancy in the Study

Women of childbearing potential are not excluded from the study as long as adequate birth control methods are being utilized or women considered post-menopausal. Women of childbearing potential are defined as fertile and physiologically capable of becoming pregnant, following menarche and until becoming post-menopausal unless permanently sterile. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. All women of childbearing potential are required to use adequate birth control methods which are summarized in the protocol's exclusion criteria and should be used during the study and continued up to 3 months post final study injection.

Prior to enrollment in the study, female subjects of childbearing potential must be advised of the importance of avoiding pregnancy during the trial and the potential risks associated with an unintentional pregnancy. During the study, female subjects are to be instructed to contact the Investigator immediately if they suspect they might be pregnant. The Sponsor must be contacted immediately and a decision will be made regarding continuation of the pregnant woman in the study based upon the circumstances surrounding the pregnancy. Pregnancy is not reportable as an AE, however, complications may be reportable and will be decided on a case by case basis. A Sponsor prepared form will be utilized to capture all pregnancy-related information until birth of the child.

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Completion of Source Documents and Case Report Forms

The nature and location of all source documents will be identified to ensure that original data required to complete the CRFs exist and are accessible for verification by the site monitor. If electronic records are maintained, the method of verification must be determined in advance of starting the study. At a minimum, source documents should include the following information for each subject:

Subject identification (name, sex, race/ethnicity)
Documentation of subject eligibility
Date of informed consent
Dates of visits
Documentation that protocol specific procedures were performed
Results of study parameters, as required by the protocol
Trial medication accountability records
Documentation of AEs and other safety parameters (if applicable)
Records regarding medical histories and the use of concomitant therapies prior to and during the study
Date of trial completion and reason for early discontinuation, if applicable

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

Electronic case report forms will be provided to the sites; only designated individuals may complete the CRFs. The CRFs will be submitted at regular intervals based upon the study visit schedule. It is expected that all data reported will have corresponding entries in the source documents and that the Principal Investigator will review the reported data and certify that the CRFs are accurate and complete. No subject identifiers should be recorded on the CRFs beyond subject number and demographic information.

13.2 Data Review and Clarifications

The CRF data will be reviewed against the subject's source data by the study monitors to ensure completeness and accuracy. After monitoring has occurred at the clinical sites and the CRFs have been submitted, additional data clarifications and/or additions may be needed. Data clarifications and/or additions are documented and are part of each subject's CRFs.

13.3 Regulatory Documentation and Records Retention

The Investigator is required to maintain up-to-date, complete regulatory documentation as indicated by the Sponsor and the Investigator's files will be reviewed as part of the ongoing study monitoring. Financial information is not subject to regulatory inspection and should be kept separately.

Additionally, the Investigator must keep study records and source documents until the Sponsor provides written approval for their destruction. If the Investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, the Sponsor must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the **latest** marketing approval).

13.4 Quality Assurance and Quality Control

The Sponsor will be responsible for implementing and maintaining quality assurance and quality control systems to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP and applicable regulatory requirements. The Sponsor will secure agreement from all involved parties to ensure direct access to all study related sites, source data and documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by domestic and foreign regulatory authorities. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements made by the Sponsor with the Investigator/Institution and any other parties involved in the study will be provided in writing as part of the protocol or as a separate agreement.

13.5 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established to monitor the safety of the trial participants, to ensure that the trial is being conducted with the highest scientific and ethical standards, and make appropriate recommendations based on the data seen.

The DMC charter will include the DMC membership and responsibilities, the timing of DMC meetings, the content of the analysis report for the DMC meetings, and the communication with the Sponsor. The DMC will only make recommendations for changes in study conduct.

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Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
02/10/2017 15:58:07	[redacted]	Biostats
02/10/2017 17:07:45	[redacted]	Management of Affected Area Approval
02/10/2017 17:16:00	[redacted]	Patient Safety