NOVARTIS

Global Clinical Development - General Medicine

RTH258/Brolucizumab

Clinical Trial Protocol [CRTH258A2301E1] / NCT03386474

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

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List of abbreviations

ADA	Anti-drug antibodies
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical (classification system)
BCVA	Best Corrected Visual Acuity
BP	Blood pressurelocal
BUN	Blood urea nitrogen
CF	Color fundus
CFR	US Code of Federal Regulations
CNV	Choroidal neovascularization
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
CSFT	Central subfield thickness
CSM	Clinical Site Management
CTM	Clincial Trial Management
EDC	Electronic Data Capture
EMA	European Medicines Agency
ETDRS	Early Treatment Diabetic Retinopathy Study
EOS	End of study
eSource	Electronic Source
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transminase
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed consent form
IEC	Independent Ethics Committee
IFU	Instructions for use
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	intrauterine system
IVT	Intravitreal injection
LDH	Lactate dehydrogenase
LFT	Liver function test
LOCF	Last observation carried forward
MedDRA	Medical dictionary for regulatory activities
nAMD	Neovascular Age-Related Macular Degeneration

OCT	Optical coherence tomography
PD	Protocol deviation
PK	Pharmacokinetics
RBC	Red blood cell
RPE	Retinal pigment epithelium
SAE	Serious Adverse Event
scFv	Single-chain variable fragment
SoC	Standard of care
SUSAR	Suspected Unexpected Serious Adverse Reactions
TD	Study Treatment Discontinuation
VA	Visual Acuity
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Subject ID	A unique number assigned to each patient upon signing the informed consent
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	RTH258A2301E1
Full Title	A 24-week, double-masked, multicenter, two-arm extension study to collect safety and efficacy data on brolucizumab 6 mg drug product intended for commercialization in patients with neovascular age-related macular degeneration who have completed the CRTH258A2301 study
Brief title	Study of safety and efficacy of brolucizumab 6 mg drug product intended for commercialization in patients with nAMD.
Sponsor and Clinical Phase	Novartis; Phase 3
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to collect data on safety and efficacy of the brolucizumab 6 mg drug product intended for commercialization in patients with nAMD and to support comparability to the 6 mg drug product used in Phase III.
Primary Objective(s)	The objective of this study is to collect data on safety and efficacy of the brolucizumab 6 mg drug product intended for commercialization in patients with nAMD previously treated in CRTH258A2301 study to support comparability to the 6 mg drug product used in Phase III.
Secondary Objectives	Not applicable
Study design	This is a 24-week, double-masked, multicenter, two-arm extension study. Patients from the United States who have completed the 96-week core study CRTH258A2301 are eligible to participate provided Visit 26/ Week 96 in the core study is ≤ 12 weeks from Baseline visit in the extension study. During the study, patients will receive either brolucizumab 6 mg (if they were treated with brolucizumab 3 mg or 6 mg in the core) or aflibercept (if they were treated with aflibercept in the core). Total study duration is 24 weeks.
Population	The study population will consist of male and female patients who have completed the CRTH258A2301 core study. Approximately 75 to 100 patients are expected to be enrolled in approximately 70 centers in the United States.
Key Inclusion criteria	• Written informed consent must be obtained before any assessment is performed.

	• The patient completed the core study, as defined by providing assessments at the Visit 26/ Week 96, within ≤ 12 weeks of Baseline visit of the extension study.
Key Exclusion criteria	1. Patient discontinued the treatment or the core study prematurely at any time. 2. Patient received standard of care treatment for nAMD after completion of the core study. 3. Any of the following treatments received after completion of the core study: • investigational treatment for nAMD in the study eye, • intraocular or periocular injections of steroids in the study eye, • systemic anti-VEGF therapy. 4. Patient has a systemic or ocular medical condition or personal circumstance which precludes study participation or compliance with study procedures, as assessed by the investigator. 5. Stroke or myocardial infarction within the 3 months of Baseline visit of the extension study. 6. 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 visit in the extension study. 7. Pregnant or nursing (lactating) women and women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 weeks after stopping of study medication.
Study treatment	• Brolucizumab 6 mg • Aflibercept 2 mg
Efficacy assessments	• BCVA • Optical coherence tomography
Key safety assessments	• Adverse event monitoring • Ophthalmic examination (intraocular pressure, slit-lamp and fundus examination) • Color fundus photography • Vital signs

	• Laboratory parameters (hematology, chemistry and urinalysis)
Other assessments	• Anti-drug antibodies • [redacted]
Data analysis	The assessment of the brolucizumab outcome of this study will be based on a within-patient comparison with corresponding core-study data serving as reference. Neither the patient selection process nor the expected sample sizes support a valid comparison between aflibercept and brolucizumab. Analyses of brolucizumab data will be performed on the Extension Safety Set which is defined as all patients who enter this extension study and receive at least one injection of study treatment. Data will be presented descriptively. No formal hypothesis testing is planned for this study. Data for the aflibercept treatment group will be presented in listings. The final analysis will be conducted on all subject data at the time the trial ends. An interim analysis may be conducted when at least 50 patients are treated with brolucizumab 6 mg for 6 months to support a brolucizumab Biologic License Application Submission at the earliest possible time point, currently planned for end of 2018.
Key words	double-masked, extension study; neovascular age-related macular degeneration; intravitreal injection; brolucizumab; aflibercept.

1 Introduction

1.1 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 (anti-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.

Brolucizumab development program in nAMD

Brolucizumab (RTH258, formerly ESBA1008) is a humanized single-chain Fv (scFv) antibody fragment inhibitor of vascular endothelial growth factor with a molecular weight of ~26 kDa. Brolucizumab 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.

The pharmacological characteristics of brolucizumab (a relatively small molecule formulated at high concentrations of 120 mg/mL) allow delivery of a much higher molar dose via intravitreal injection compared to other VEGF-inhibitors. A 6 mg dose of brolucizumab delivers a molar dose which is approximately 11 and 22 times higher than aflibercept 2 mg and ranibizumab 0.5 mg, respectively. These attributes are expected to confer advantages in the treatment of retinal diseases. A low molecular weight and high concentration gradient between the vitreous and the retina should increase drug distribution into the target site of action, ensuring rapid and effective control of anatomical disease activity.

Safety, efficacy, and pharmacokinetics of brolucizumab in patients with nAMD were evaluated in the following completed clinical studies:

- Single ascending dose study of brolucizumab (0.5, 3.0, 4.5 and 6 mg) versus ranibizumab 0.5 mg (Alcon protocol C-10-083),
- 56-week multiple dose study of brolucizumab 6 mg versus aflibercept 2 mg (Alcon protocol C-12-006),
- Proof-of concept study of two concentrations of brolucizumab (120 mg/mL and 60 mg/mL) applied as a microvolume injection (10 µL) or infusion (8.3 µL) (Alcon protocol C-13-001),
- 3 dose study of brolucizumab 6 mg or 3 mg in patients of Japanese and non-Japanese ancestry (Alcon protocol RTH258-E003 also referred to as CRTH258A2201).

Brolucizumab was demonstrated to be safe and well tolerated with an ocular and systemic safety profile similar to ranibizumab and aflibercept and non-inferior efficacy as compared to ranibizumab and aflibercept. Please refer to the Investigator's Brochure (IB) for further details

Two pivotal, two-year, randomized, double masked, multicenter phase III studies of brolucizumab are ongoing in patients with nAMD: CRTH258A2301 (HAWK) and CRTH258A2302 (HARRIER). The primary objective of both studies is to demonstrate noninferiority of brolucizumab to aflibercept. Please refer to the study protocols for additional details. In a recently performed analysis of data up to Week 48 non-inferiority of brolucizumab 3 mg and 6 mg versus aflibercept 2 mg in mean change in best-corrected visual acuity (BCVA) from baseline to Week 48 was demonstrated. The non-inferiority in BCVA occurred while the majority of patients on 6 mg brolucizumab (57% (HAWK) and 52% (HARRIER) were maintained exclusively on a q12 regiment immediately following the loading phase through week 48 versus q8 regimen for aflibercept. Brolucizumab was generally well tolerated with overall ocular and non-ocular (systemic) adverse event rates comparable to aflibercept.

Drug substance and drug product manufacturing changes have been implemented for brolucizumab in order to scale-up the manufacturing process and to modify the brolucizumab formulation intended for commercialization, respectively.

During the Type C meeting with FDA on September 20, 2017, the FDA recommended to include into the Biologic License Application clinical data of at least 50 patients (who were previously treated with brolucizumab in ongoing HAWK and/or HARRIER studies) treated for additional 6 months with the brolucizumab product intended for commercialization to support comparability.

This study, CRTH258A2301E1, is an extension of the CRTH258A2301 (HAWK) study. Patients from US completing Visit 26/ Week 96 of HAWK will be eligible to participate. All enrolled patients will receive either brolucizumab 6 mg (if previously treated with brolucizumab 3 mg or 6 mg) or aflibercept 2 mg (if previously treated with aflibercept 2 mg) over a study period of 24 weeks. At least 50 patients previously treated with brolucizumab will be enrolled into the extension study.

1.2 Purpose

The purpose of this study is to collect information on safety and efficacy of the brolucizumab 6 mg drug product intended for commercialization in patients with nAMD to support comparability to the brolucizumab 6 mg drug product used in Phase III clinical studies.

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
• To collect data on safety and efficacy of the brolucizumab 6 mg drug product intended for commercialization in patients with nAMD previously treated in CRTH258A2301 study to support comparability to the brolucizumab 6 mg drug product used in Phase III clinical studies	• Incidence and characteristics of treatment emergent adverse events • Loss in BCVA of 15 letters or more from Baseline at each post-baseline visit • Change in BCVA from Baseline at each post-baseline visit • q12 treatment status at Week 20 • Change in CSFT from Baseline at each post-baseline visit • ADA status at Baseline, Week 8, Week 16 and Week 24.

3 Investigational plan

3.1 Study design

This is a double-masked, multicenter, two-arm extension study (Figure 3-1). Subgroup of patients who have completed the 96-week core study CRTH258A2301, regardless of the treatment group (brolucizumab 3 mg, brolucizumab 6 mg or aflibercept 2 mg) are eligible for inclusion in the extension provided Visit 26/ Week 96 in the core study is ≤ 12 weeks from Baseline visit in the extension study. Patients who were treated with aflibercept during the core study will continue to receive aflibercept in the extension study. Patients who were treated with brolucizumab 3 mg or 6 mg in the core study will receive brolucizumab 6 mg in the extension study.

At the Baseline visit, patients will sign an informed consent and will be evaluated for study eligibility based on inclusion/exclusion criteria.

Baseline visit

Baseline visit of the extension study must occur no later than 12 weeks after Visit 26/ Week 96 of the core study.

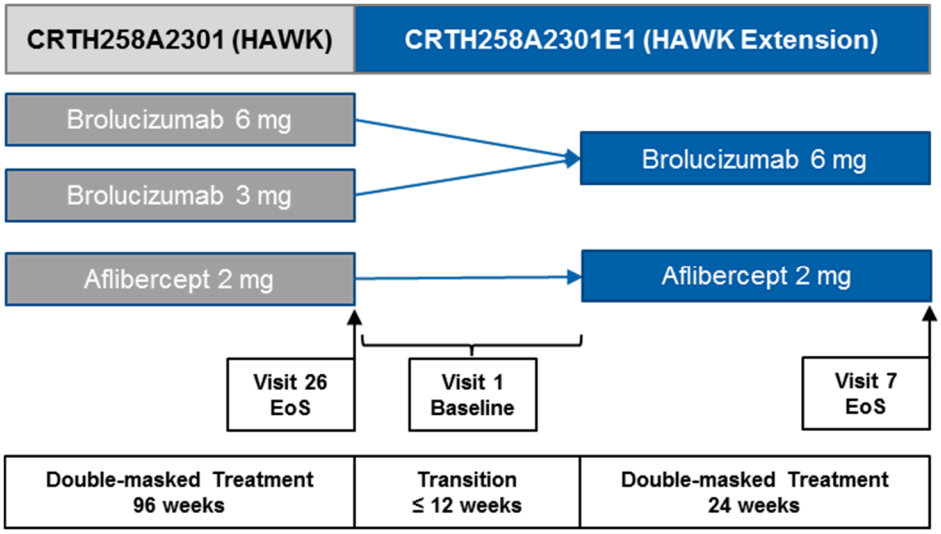
If the patient can directly rollover from the core to the extension study, Baseline visit of the extension study can occur on the same day as the Visit 26/Week 96 of the core study.

If the patient already completed Visit 26/Week 96 in the core study, Baseline visit of the extension study should occur as soon as possible and no later than 12 weeks after Visit 26/Week 96 of the core study.

Enrolled patients will receive three intravitreal injections of either brolucizumab 6 mg or aflibercept 2 mg according to dosing schedule described in Section 5.5.4. This extension study consists of 7 study visits at 4-week intervals, labeled Visit 1/ Baseline to Visit 7/ EoS over a period of 24 weeks.

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

Figure 3-1 Study design



3.2 Rationale for study design

This multicenter extension study is designed to collect data on safety and efficacy of the brolucizumab 6 mg drug product intended for commercialization in nAMD patients. Enrollment of patients who were treated with aflibercept in the core study ensures that the conduct of both studies (core and extension) remains double-masked in a seamless fashion and until the end of each study. Study design, study duration and patient population were assessed as adequate to gain safety and efficacy experience with brolucizumab 6 mg drug product intended for commercialization.

The patient population will be described in more detail in Section 4 below.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

Analysis of the data up to Week 48 from the ongoing CRTH258A2301 and CRTH258A2302 studies demonstrated non-inferiority in BCVA for brolucizumab as compared to aflibercept while the overall ocular and non-ocular (systemic) adverse events were comparable between the two treatments.

Patients entering this extension study who were treated with brolucizumab 3 mg or 6 mg in the core study will receive three brolucizumab 6 mg IVT injections: at Baseline, Week 8 and, depending on the disease activity status, at Week 16 (q8 interval) or Week 20 (q12 interval). This is to ensure that patients, regardless of treatment regimen in the core study (i.e., q12 or q8)

are not under-treated. Patients entering this extension study who were treated with aflibercept 2 mg in the core study will continue to receive aflibercept 2 mg every 8 weeks as per approved label. Since patients have been previously treated in HAWK study at maintenance treatment frequencies of q12 or q8, treatment initiation within this extension study starting with fixed treatment at Baseline and Week 8 is considered adequate.

3.4 Rationale for choice of comparator

In the CRTH258A2301 core study, efficacy and safety of brolucizumab was compared with aflibercept.

This is an extension to the CRTH258A2301 study and patients who were randomized to the aflibercept arm in the core will continue receiving aflibercept in order to ensure that both studies (core and extension) remain double-masked in a seamless fashion and until the end of the extension study.

For the assessment of the outcome of this extension study, the core study data for patients participating in this extension study will be used as a reference.

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis might be conducted when 50 patients are treated with brolucizumab 6 mg for 6 months to support a brolucizumab Biologic License Application submission at the earliest possible time point, which is currently planned for Dec 2018.

3.6 Risks and benefits

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

Comprehensive analytical drug substance comparability studies and ongoing analytical testing of the drug product, demonstrate comparability between drug substance/product used in ongoing Phase III clinical studies and the drug substance intended for commercialization. Results from this study will support comparability between brolucizumab 6 mg drug product intended for commercialization and used in Phase III studies.

In a recently performed analysis of data up to Week 48, non-inferiority of brolucizumab 3 mg and 6 mg versus aflibercept 2 mg in mean change in BCVA from baseline to Week 48 was demonstrated. The non-inferiority in BCVA occurred while the majority of patients on 6 mg brolucizumab, 57% (HAWK) and 52% (HARRIER), were maintained exclusively on a q12 regiment immediately following the loading phase through week 48 versus q8 regimen for aflibercept.

Further details of the known and potential risks and benefits associated with brolucizumab are presented in the Investigator's Brochure.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

4 Population

The study population will consist of male and female patients who have completed the core study (CRTH258A2301). Approximately 75 to 100 patients are expected to be enrolled in approximately 70 centers in the United States.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. The patient completed the core study, as defined by providing assessments at the Visit 26/ Week 96, within ≤ 12 weeks of Baseline visit of the extension study.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Patient discontinued the treatment or the core study prematurely at any time.
2. Patient received standard of care treatment for nAMD after completion of the core study.
3. Any of the following treatments received after completion of the core study:
    a. investigational treatment for nAMD in the study eye,
    b. intraocular or periocular injections of steroids in the study eye,
    c. systemic anti-VEGF therapy.
4. Patient has a systemic or ocular medical condition or personal circumstance which precludes study participation or compliance with study procedures, as assessed by the investigator.
5. Stroke or myocardial infarction within the 3 months of Baseline visit of the extension study.
6. 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 visit in the extension study.

    Note: observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary.
7. Pregnant or nursing (lactating) women and women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 weeks after stopping of study medication. Highly effective contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

c. Male sterilization (at least 6 m prior to screening in the core study). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject

d. Use of oral, (estrogen and progesterone), 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 or placement of an intrauterine device (IUD) or intrauterine system (IUS)

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the ICF.

Women are considered post-menopausal and not of child bearing potential 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), total 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.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

- Brolucizumab 6 mg
- Aflibercept 2 mg

Brolucizumab 6 mg drug product intended for commercialization is used in this study. Changes to the excipients within the drug product were made, namely change to the pH (increase from app. 6.8 to app. 7.2) and change to the polysorbate concentration (decreased in concentration from 0.05% to 0.02%). Although drug substance remains unchanged, an optimized manufacturing scale for brolucizumab drug substance was introduced.

Brolucizumab study kits will consist of a carton that contains 1 single use, sterile glass vial containing approximately 0.2 mL of the brolucizumab solution to allow the administration of a single dose (50 µL) and a single filter needle. The content of the vial must not be split. The formulation does not contain any preservative; it is to be used for single-dose administration only. The proposed commercial instructions for use (IFU) of the brolucizumab kit are provided in the Operational Manual.

Novartis will provide sufficient supplies of brolucizumab for treatment use to allow for completion of the study.

The aflibercept trial kits will consist of a masked, numbered carton containing the following items depending on the source of the aflibercept:

- Novartis-sourced aflibercept: one package of aflibercept in its commercial presentation and one post-injection label containing the same kit number as the carton mentioned above. The post-injection label will be placed on the vial of aflibercept after injection. Novartis will provide sufficient supplies of aflibercept for treatment use to allow for completion of the study.
- Site-sourced aflibercept: One post-injection label containing the same kit number as the carton mentioned above. The post-injection label will be placed on the vial of aflibercept after injection. The labeled vial and the commercial carton will be placed inside the numbered carton mentioned above.

All aflibercept for this study will be sourced using only one of the two options outlined above. Sourcing the aflibercept using both options will not be allowed.

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.

5.1.2 Additional treatment

No additional treatment beyond investigational drug is included in this trial.

5.2 Treatment arms

Depending on the treatment arm assignment in the core study, patients will be assigned at Visit 1/ Baseline to one of the two treatment arms:

- **Arm 1: brolucizumab 6 mg** – patients treated with brolucizumab 3 mg or brolucizumab 6 mg in the core study. All patients will receive IVT injection at Baseline and Week 8 and, depending on disease activity as assessed by the investigator, at Week 16 or Week 20.
- **Arm 2: aflibercept 2 mg** – patients treated with aflibercept 2 mg in the core study. All patients will receive IVT injection at Baseline, Week 8 and Week 16.

5.3 Treatment assignment and randomization

At Visit 1/ Baseline, the investigator or his/her delegate will access the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. IRT will specify a unique medication number for the package of study drug to be dispensed to the patient.

5.4 Treatment masking

This is a double-masked study. The patients, investigators and site staff (except for the unmasked site personnel and unmasked injecting physician), Sponsor clinical site management (except for those who have been delegated responsibility for working with the study drug), the

statisticians and clinicians who are 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 using the following methods:

- Sponsor personnel who has access to treatment codes (e.g., unmasked Programming personnel directly involved in bioanalysis of serum samples, unmasked monitors performing study drug accountability, Clinical Supplies personnel, members of the HAWK study team having access to week 48 subject level data) will not divulge the codes to subjects, Investigators, site staff, Sponsor Clinical Trial Management (CTM), or Sponsor Clinical Site Management (CSM).
- Treatment allocation data will be kept strictly confidential until the time of unmasking, and will not be accessible by anyone else involved in the study.
- Study drug injections will be performed by unmasked injecting physician.
- Sham injections will be administered to establish identical injection schedule in both treatment arms.

To maintain the masking and data integrity at least two investigators (and corresponding study staff) will be involved in the study at each site: one masked (evaluating) investigator performing all assessments and capturing data in the EDC and one unmasked (treating) investigator administering study treatment according to the protocol. The investigators will maintain the same role throughout the study. The unmasked investigator in the core study cannot resume responsibilities of the masked investigator in the extension study and vice versa.

The **Masked Investigator** is masked to the treatment assignment and performs the monthly clinical assessments. All other site staff involved in performing study assessments and procedures (e.g. BCVA, ophthalmic examination, disease activity assessments, upload of data in eCRF) must be also masked to the treatment assignment. The only exception is the administration of study treatment and post-injection assessment (see below).

The **Unmasked Investigator** performs the injections and will be unmasked to the treatments as will any other site personnel who have delegated responsibility for working with the study drug. The unmasked physician and other site personnel must not perform any other roles after randomization except the assessment of safety immediately following IVT injection.

The masked/evaluating Investigator will be responsible for all aspects of the study, excluding the injection procedures. The unmasked/treating Investigator will only perform all treatment/sham injections and must not be involved in any other aspects of the study and must not divulge the patient treatment assignment to anyone (masked site personal, the patient and the masked Sponsor representative). Once the designated roles are determined, the roles cannot be switched at any time during the conduct of the study. Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this masked study.

VA examiner (masked to the treatment assignment)

A trained and certified (by Novartis designated VA Certifier) site clinical staff with optometrical training. The VA examiner will not perform any tasks which may unmask him or her to patient's treatment.

The detailed list of study tasks performed by masked and unmasked Investigators and Site Personnel is provided in the Operation Manual.

Unmasked sponsor personnel will include unmasked monitors performing study treatment accountability and reporting protocol deviations requiring knowledge of treatment allocation. Unmasked CTM and unmasked statistician will be involved in assessment of those unmasked PDs.

Unmasking will only occur in the case of patient emergencies (see Section 5.6), at the time of the interim analysis if performed (see Section 3.5) and at the conclusion of the study. Interim analyses will be performed with an unmasking of specified individuals from the sponsor who are not directly involved in the conduct of the trial (see Section 9.7).

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number assigned by Novartis. The subject number is composed of a site number and a sequential number.

The same Subject Number assigned to the patient in the core study will be used in the extension study.

Upon signing the informed consent form, the investigator or his/her staff will access the IRT and provide the requested identifying information for the patient to register them into the IRT. This information includes subject number that was assigned to the patient in the core study.

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the appropriate Screening period CRF.

5.5.2 Dispensing the study drug

Each study site will be supplied with investigational and control drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label. Investigator staff will identify the study drug package(s) to dispense to the patient by accessing the IRT and obtaining the medication number(s). Immediately before administration of the IVT injection to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees

have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

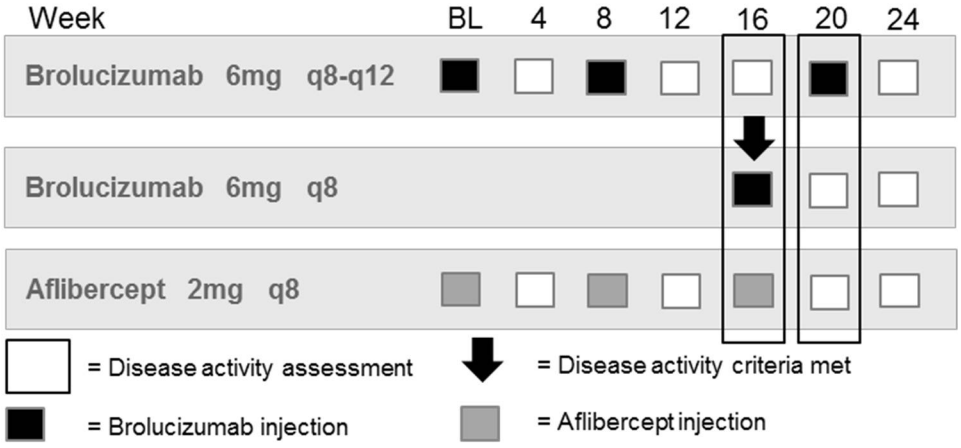
5.5.4 Instructions for prescribing and taking study treatment

Brolucizumab will be administered via intravitreal injection (in accordance with supplied proposed commercial instructions for use as described in the Operational Manual) at Visit 1/ Baseline, Visit 3/ Week 8, and, depending on the disease activity as assessed by the investigator, at Visit 5/ Week 16 or Visit 6/ Week 20.

Aflibercept will be administered via intravitreal injection at Visit 1/ Baseline, Visit 3/ Week 8, and Visit 5/ Week 16.

Sham injection will be administered at Visit 5/ Week 16 to patients on brolucizumab 6 mg q12 interval (without disease activity at Week 16 as assessed by the investigator) and at Visit 6/ Week 20 to patients on aflibercept 2 mg or patients on brolucizumab 6 mg q8 interval (with disease activity at Week 16 as assessed by the investigator).

Figure 5-1 Dosing schedule



Disease activity assessment

Disease activity will be assessed by the investigator at Visit 5/ Week 16 and Visit 6/ Week 20.

The investigators should apply their own expert judgement when assessing disease activity i.e., q8 treatment need. Decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with Week 12 might be considered as guidance.

Intravitreal injection

The IVT injection will be carried out under controlled, aseptic conditions per local clinical practice and following the processes provided in core study.

The study eye will be assessed before and after intravitreal injection to ensure that the procedure and/or the study treatment had not endangered the health of the eye.

An IVT injection is contraindicated in patients with active ocular or periocular infections and in patients with active intraocular inflammation; therefore, the investigator should verify that these conditions are not present in either eye (study and fellow eyes) prior to every injection.

All kits of study treatment assigned by the IRT will be recorded/ databased in the IRT.

Date and time of every injection administered to the patient will be recorded in the CRF.

At selected sites, the conduct of IVT injections will be observed by an external study team member to ensure compliance with the proposed commercial instruction for use.

Sham injection

At Visit 5/ Week 16 or Visit 6/ Week 20, sham injection will be administered to maintain masking. For the sham injection, the tip of an injection syringe (the hub without a needle) will be used.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational treatment dose adjustments are not permitted.

If based on investigator's judgement, safe administration of the study drug is contraindicated (e.g., patient experiences an AE), investigational treatment can be administered within 7 days after the scheduled visit or temporarily interrupted.

5.5.6 Rescue medication

Rescue medication in the study eye is not permitted in this study.

Treatment with medications approved for nAMD is permitted in the fellow eye at the discretion of the investigator and in accordance with the administration procedures established at the study center. Such treatment must be recorded on the appropriate CRF.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the appropriate CRF.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before enrolling a patient or allowing a new medication to be started.

5.5.8 Prohibited medication

Use of the treatments displayed in the below table is NOT allowed after the start of investigational drug.

Table 5-1 Prohibited medication

Medication	Prohibition period	Action taken
Study eye		
Anti-VEGF therapy other than IP	Any time	Discontinue study treatment
Intraocular or periocular injections of corticosteroids (except if treatment for AE)	Any time	Discontinue study treatment
Laser treatment for AMD	Any time	Discontinue study treatment
Fellow eye		
Investigational treatment	Any time	None
Systemic		
Anti-VEGF therapy	Any time	Discontinue study treatment
Any investigational drug, biologic or device (with the exception of over-the-counter vitamins, supplements or diets)	Any time	Discontinue study treatment

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment

assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that unmasking can be performed at any time.

After treatment unmasking the patient cannot continue to receive the assigned treatment and if applicable will be given standard of care as per investigator judgement.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

The investigator and/or referring physician will recommend the appropriate follow-up medical care, if needed, for all patients who completed the study or prematurely withdrawn from the study.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.6 and Section 7.6)
- Use of prohibited treatment as per recommendations in Table 5-1
- Any situation in which study participation might result in a safety risk to the patient
- At the investigator's discretion based on his/her clinical judgement the patient requires rescue medication

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The investigator should encourage the patient to continue in the study and to return for the remaining visits up to and including Visit 7/ EoS. Otherwise, the patient should return to the clinic as soon as possible, after discontinuation of study drug, for an EoS visit. EoS visit assessments detailed in Table 6-1 should be completed and recorded in the CRF.

The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the appropriate CRF.

The investigator must also access the IRT to register the patient's discontinuation from study treatment.

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table below.

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her planned end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely discontinued patient. 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 Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Patients must be seen for all visits on the designated day, or as close to it as possible. Patients with missed visits should have them re-scheduled as soon as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

Table 6-1 Assessment schedule

Visit number	**1/ Baseline[a]**	**2**	**3**	**4**	**5**	**6**	**7/ EoS[l]**
Week	**Day 1**	**4**	**8**	**12**	**16**	**20**	**24**
Visit window (days)		**+/- 7**	**+/- 7**	**+/- 7**	**+/- 7**	**+/- 7**	**+/- 7**
Informed consent[b]	X						
Inclusion/Exclusion Criteria	X						
Demographics	X						
Medical History	X[c]						
Urine Pregnancy Test[d]	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X[n]	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Chemistry/ Hematology/ Urinalysis[ef]	X						X
Anti-Drug Antibodies (ADA)	X		X		X		X
[redacted]							
BCVA[h]	X	X	X	X	X	X	X
Slit-lamp and Fundus Exam[f]	X[o]	X	X	X	X	X	X[o]
Intraocular Pressure (IOP)	X[o]	X	X	X	X	X	X[o]
Optical Coherence Tomography[i]	X[o]	X	X	X	X	X	X[o]
Color Fundus Photography[fi]	X						X
Access IRT	X		X		X	X	
Disease Activity Assessment					X	X	
IVT injection[m] and post-injection assessment[fg]	X		X		X[j]	X[k]	

a – Visit 1/ Baseline of CRTH258A2301E1 can occur on the same day as the patient's last visit in CRTH258A2301 (Visit 26/ Week 96) but no later than 12 weeks after Visit 26/ Week 96 of CRTH258A2301

b – ICF must be obtained prior to any study specific procedure

c – When Baseline visit of the extension study does not occur on the same day as the last visit in the core study, medical conditions which started and/or ended after the last visit in the core and before the baseline visit in the extension study will be recorded

d – Women of childbearing potential only. Urine pregnancy tests will be performed unless local regulations require a serum pregnancy test

e – All blood draws should be performed prior to receiving the IVT injection

f – These assessments are source documentation only and will not be entered into the CRF

g – The study eye will be evaluated within 5 minutes and approximately 30 minutes post injection to ensure that the injection procedure and/or the investigational product have not endangered the health of the eye

h – Both eyes at all visits

i – Local assessments (no central reading center)

j – Only if patient assigned to q8

k – Only if patient assigned to q12

l – All procedures should be followed, regardless of when the patient exits the study

m – At selected sites, the conduct of IVT injections will be observed by an external study team member to ensure compliance with the proposed commercial instruction for use

n – Adverse Events which are ongoing at the patient's last visit in CRTH258A2301 and at the baseline visit in the extension study must be recorded and entries in the extension study database should match those in the core study database as appropriate

o – Both eyes; all other assessments are study eye only

6.1 Information to be collected on screening failures

There is no separate screening visit/ screening period planned in this study. Patient's eligibility will be assessed at Visit 1/ Baseline.

All patients who have signed informed consent but not entered into the extension study will be considered screen failures. The following information will be collected for screen failure patients: demographics, inclusion/exclusion, and serious adverse event (SAE). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: age, sex, race, ethnicity, and Japanese ancestry, study eye, iris color and history of primary diagnosis. With the exception of age, entries in the extension study database should match those in the core study database.

Additionally, the following data will be collected for all patients at baseline: vital signs, BCVA, IOP, and concomitant medications.

For patients whose baseline visit of the extension study does not occur on the same day as the last visit in the CRTH258A2301 core study, medical condition which started and/or ended after the last visit in the core study and before the baseline visit in the extension study will be collected.

6.3 Treatment exposure and compliance

Every time the study treatment is to be administered, IRT needs to be accessed for the medication (kit) number. The date and time of all study treatment injections administered during the study and any deviations from the protocol treatment schedule will be recorded in the CRF Dosing Log and/or will be captured by the unmasked field monitor.

Exposure to the study treatment will be based on the number of injections administered. Compliance with the study treatment will be assessed by the unmasked field monitor at each visit using vial counts and information provided by the pharmacist or by the investigator.

The type, reason for use, start and stop dates (or "ongoing") of all concomitant medications administered during the study will be collected on the Concomitant medications CRF.

6.4 Efficacy

Efficacy assessment will include BCVA with ETDRS-like chart at 4 meters and Optical Coherence Tomography (OCT).

The BCVA will be conducted in both eyes at every study visit. BCVA testing should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye, or administration of study treatment.

6.4.1 Visual acuity assessment

Best-corrected visual acuity will be tested at all study visits in a sitting position using the ETDRS visual acuity testing protocol at an initial testing distance of 4 meters.

If it is not possible to perform a subjective refraction or VA testing at 4 meters because VA is too poor for the patient to read at least 4 letters on the EDTRS chart at this distance, the refraction/VA testing should be attempted at 1 meter. Further details on refraction technique and VA testing will be described in the Operational Manual, which will be provided to all sites.

Certificates from the core study will be extended for investigators and/or their designated study staff performing VA assessments as well as all the equipment. New staff will be certified for this trial by Novartis designated VA certifiers.

The total BCVA score derived according to the Operational Manual captured in the VA Assessment Worksheet will be recorded in the CRF.

6.4.2 Optical Coherence Tomography

Optical Coherence Tomography will be assessed in the study eye at every study visit and in both eyes at Visit 1/ Baseline and Visit 7/ EoS.

The assessment will be performed by qualified technician or investigator prior to study drug administration. The investigator should evaluate the images according to their standard clinical practice and capture Central Subfield Thickness (CSFT) in the CRF. No other qualitative or quantitative parameters will be collected. Any new clinically significant abnormalities after Baseline will be recorded on the adverse event page of the CRF.

All OCT images will be retained in source documents. The sponsor may request OCT images to be submitted for the central review, if standardized evaluation is deemed necessary.

6.4.3 Appropriateness of efficacy assessments

BCVA and OCT are standard assessments for this indication and patient population, and well established in the field of ophthalmologic clinical research.

6.5 Safety

Safety assessments will be done based on ophthalmic examinations, color fundus photography, vital signs, laboratory results and the type, frequency, and severity of AEs.

Safety assessments are performed according to the schedule in Table 6-1.

6.5.1 Ophthalmic examination

The ophthalmic exam will be performed in the study eye at every study visit and in both eyes at Visit 1/ Baseline and Visit 7/ EoS. If study visit assessments and a corresponding treatment occur on separate days, ophthalmic examinations should be performed as safety check-up before treatment of the eye.

The ophthalmic exam will consist of the following:

- **Slit-lamp examination (Bimicroscopy)** – includes evaluation of the lids/lashes, conjunctiva, cornea, anterior chamber aqueous reaction (cells and flare), iris, lens and anterior part of the vitreous body. Slit-lamp examination will be performed before study treatment. The test results will be recorded in the source documents only and any clinically significant findings must be documented on the CRF.

- **Intraocular pressure measurement (IOP)** – a measurement of IOP will be conducted using an applanation tonometer or Tonopen. The same method should be used throughout the study for each patient. If dilation is required, IOP must be measured prior to the use of dilating drops. The IOP will be assessed pre-dose and post-dose at every scheduled visit. The values recorded in mmHg will be entered into the CRF.

  In case of any abnormal rise of intraocular pressure (≥25 mmHg), if not transient, for any reason and at any time during the study period, treatment and closer monitoring of IOP should be performed by the investigator in order to achieve similar values to the baseline measurement. In this case, intravitreal procedure is not recommended unless normalization of the IOP has been achieved. The investigator should treat appropriately the increased IOP in order to allow the patient to continue in the study.

  Monitoring of optic nerve head perfusion may be appropriate within 30 minutes after injection, at the discretion of the investigator and/or according to the local requirements/practices. Results of these procedures will be recorded in the source documents, only if the findings constitute an AE they have to be recorded in the AE CRF.

- **Fundus exam** – includes ophthalmoscopic assessments of the vitreous, retina, macular, choroid, and optic nerve. The retina will also be assessed for detachment/tear and hemorrhage and the vitreous will be evaluated for hemorrhage and vitreal cells. Dilation for the fundus exam is at the discretion of the investigator. Fundus examination will be performed before study treatment and recorded in source documentation. Any clinically significant findings must be documented on the CRF.

6.5.2 Color Fundus Photography

Color Fundus (CF) photography will be assessed in the study eye at Visit 1/ Baseline and Visit 7/ EoS.

The assessment will be performed by qualified technician or investigator prior to study drug administration. The investigator should evaluate the images according to their standard clinical practice and record any clinically significant abnormalities on the adverse event page of the CRF.

A copy of the photographs will be retained in the source documents. The sponsor may request CF photographs to be submitted for the central review, if standardized evaluation is deemed necessary.

6.5.3 Vital signs

Vital signs include blood pressure (BP) and pulse measurements. After the patient has been sitting for approximately five minutes (in case of ‘white coat syndrome’ the patient should be given sufficient time to calm down), with back supported and both feet placed on the floor, systolic and diastolic BP will be measured three times using an automated validated device, with an appropriately sized cuff. The repeat sitting measurements will be made at approximately 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

On days when study drug is administered, vital signs will be measured before administration of study medication.

6.5.4 Laboratory evaluations

Local or central laboratory will be used for analysis of all specimens collected at the visits indicated in Table 6-1. The results of the laboratory examinations should be recorded in the source documents only. Any clinically significant abnormalities will be recorded on the adverse event page of the CRF.

Whether action needs to be taken to address notable laboratory values will be decided by the study investigator, taking into account the overall status of the patient. No specific action is foreseen as part of the study protocol.

6.5.4.1 Hematology

Hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute and percentage of neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and quantitative platelet count will be measured.

6.5.4.2 Clinical chemistry

Blood urea nitrogen (BUN), serum creatine, BUN/Creatinine ratio, uric acid, cholesterol, triglycerides, albumin, total globulin, albumin/globulin (A/G) ratio, total serum iron, total protein, serum electrolytes (sodium, potassium, bicarbonate, chloride, calcium, magnesium), phosphate, glucose and the following liver function tests (LFTs): serum aspartate transaminase [AST (SGOT)], serum alanine transaminase [ALT (SPGT)], alkaline phosphatase, gamma glutamyl transminase (GGT), total bilirubin, direct bilirubin, indirect bilirubin, and lactate dehydrogenase (LDH) will be measured.

6.5.4.3 Urinalysis

Specific gravity, pH, color, glucose, blood, ketones, bilirubin, and microscopic examination (WBC, RBC, epithelial cells, bacteria, mucus, casts, crystals) will be performed.

6.5.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

A urine pregnancy test will be conducted for all women of childbearing potential to assess pregnancy before inclusion into the study (Visit 1/ Baseline) and at Visit 7/ EoS. During the study, monthly urine pregnancy testing will be performed.

6.5.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

6.6 Other assessments

6.6.1 Anti-drug antibodies (immunogenicity)

Collection of blood for ADA assessment will be performed at Visit 1/ Baseline, Visit 3/ Week 8, Visit 5/ Week 16 and Visit 7/ EoS. Blood draws should take place prior to the study drug administration.

Further details on sample collection, numbering, processing, storage and shipment can be found in the Central Laboratory Manual.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events.

Adverse events must be recorded in the appropriate CRF capturing AEs under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity AE grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to
  - the study treatment
  - the ocular injection procedure
- its duration (start and end dates or actual duration if AE was shorter than 24 hours) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding [investigational] treatment
- for ocular AEs, the eye the AE occurred in

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's

source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit / following the last administration of study treatment whichever is later must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit / following the last administration of study treatment should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study 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.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

7.3 Liver safety monitoring

Due to the extremely low systemic exposure following IVT administration and the lack of systemic toxicity following repeated IVT injections of brolucizumab up to 6 mg observed in pre-clinical studies, no clinical liver toxicity studies were considered necessary. In addition, clinical experience with other intravitreally administered VEGF-inhibitors did not identify any liver safety concern.

Laboratory assessments will be performed at Visit 1/ Baseline and Visit 7/ EoS. Please refer to Section 6.5.4 and Section 6.5.4.2 for details and list of laboratory parameters that will be measured.

7.4 Renal safety monitoring

Due to the extremely low systemic exposure following IVT administration and the lack of systemic toxicity following repeated IVT injections of brolucizumab up to 6 mg observed in pre-clinical studies, no clinical renal toxicity studies were considered necessary. In addition, clinical experience with other intravitreally administered VEGF-inhibitors did not identify any renal safety concern.

Laboratory assessments will be performed at Visit 1/ Baseline and Visit 7/ EoS. Please refer to Section 6.5.4 and Section 6.5.4.2 and 6.5.4.3 for details and list of laboratory/urine parameters that will be measured.

7.5 Reporting of study treatment errors

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse/ abuse is not applicable to this study as IVT injection is performed by the investigator.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the Dosing CRF (date and time of the injection) and in the Dispensing Log at the Study site, irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

Table 7-1 Guidance for capturing the study treatment errors

Treatment error type	Document in CRF (Yes/No)	Dispensing Log (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes (only date and time of injection)	Yes (misallocation, e.g. patient received wrong medication)	Only if associated with an AE	Only if associated with an SAE

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis clinical research associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. [Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs.] The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs) using fully validated secure web-enabled software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After

database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO).

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

The assessment of the brolucizumab outcome of this study will be based on a within-patient comparison with corresponding core-study data serving as reference. Neither the patient selection process nor the expected sample sizes support a valid comparison between aflibercept and brolucizumab. Analyses of brolucizumab data will be performed on the Extension Safety Set which is defined as all patients who enter this extension study and receive at least one injection of study treatment. Data will be presented descriptively. No formal hypothesis testing is planned for this study. Data for the aflibercept treatment group will be presented in listings.

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

All analyses will be presented for the brolucizumab 6 mg treatment group. Selected analyses may be presented stratified by core study treatment group (brolucizumab 6 mg, brolucizumab 3 mg). Data for aflibercept patients will be presented in separate listings.

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

9.1 Analysis sets

All analyses will be performed on the Extension Safety Set, being defined as all patients who enter this extension study and receive at least one injection of study treatment in this extension study.

9.2 Patient demographics and other baseline characteristics

9.2.1 Demographics

Age (< 50, 50-64, 65-74, 75-84, ≥ 85 years), gender, ethnicity and Japanese ancestry will be summarized using the number of observations, the number of observations for each category and the corresponding frequency and percent.

Age will also be summarized as a continuous variable.

9.2.2 Baseline characteristics

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

A summary of length of time (weeks) between the last visit of the core study and first visit of extension study will be presented.

9.2.3 Medical history

Medical history (ocular and non-ocular) will be described based on:

- the medical history as documented in the core study
- all treatment emergent SAEs/AEs as documented in the core study
- all new medical conditions occurring between the end of core study and enrollment into the extension study

Tabulations will be based on primary system organ class and preferred term according to the MedDRA dictionary.

9.3 Treatments

9.3.1 Study treatment exposure

The extent of exposure to study treatment is calculated using the number of injections. The following summaries will be presented:

- Overall number of treatments will be presented separately (active and sham, active only, sham only) during the following time periods:
  - Extension baseline to Week 8
  - Week 12 to Week 24
  - Extension baseline to Week 24
- Treatment exposure by visit: The number and percent of patients who received active injections, sham injections, missed a treatment (active and sham) and missed visits will be presented by visit and by treatment status (q8, q12)
- Frequency of all observed dosing patterns from extension baseline to Week 24 differentiating between active and sham treatments, missed treatments and wrong treatments will be presented
- brolucizumab q12/q8 allocation by visit: Number and percent of patients on q12 and q8 at each visit

9.3.2 Prior medications

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

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

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

9.3.3 Prior surgical and medical procedures

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

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

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

9.3.4 Concomitant medications

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

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

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

9.3.5 Concomitant surgical and medical procedures

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

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

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

9.4 Analysis of safety and efficacy variable(s)

The objective of this study is to collect data on the safety and efficacy of the brolucizumab 6 mg drug product intended for commercialization in patients with nAMD previously treated in the CRTH258A2301 study to support comparability to the drug product used in Phase III. The aflibercept 2 mg treatment arm is included in this study to maintain the masking. Correspondingly, the analysis will focus on brolucizumab patients only. Data of aflibercept patients will be presented in separate listings.

9.4.1 Safety and efficacy variable(s)

Safety and efficacy variables:

- Treatment emergent Adverse Events
- Best-corrected visual acuity
- q12 treatment status at Week 20
- ADA status including drug exposure
- CSFT
- Intraocular pressure
- Vital signs

9.4.2 Statistical model, hypothesis, and method of analysis

Formal hypothesis testing is not planned for this study.

Treatment emergent Adverse Events

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

The number and percentage of patients who report treatment emergent AEs will be summarized by primary system organ class and preferred term according to the MedDRA dictionary. Separate summaries will be produced for ocular and non-ocular events. Ocular AEs will be presented for the study eye and fellow eye separately.

In addition, the following treatment emergent AE summaries will be produced:

- SAEs by primary system organ class and preferred term
- AEs by maximum severity, primary system organ class and preferred term
- AEs resulting in treatment and/or study discontinuation by primary system organ class and preferred term
- AEs (as defined in the case retrieval strategy) by safety topic of interest and preferred term
- AEs by causal relationship to study treatment and ocular injection procedure

AEs which start prior to the date/time of the first injection of study treatment in this extension study will be listed only.

Treatment emergent AEs occurring during the last 6 months of the core study, for the same set of patients included in the extension study safety set will be presented.

Best-Corrected Visual Acuity

The change from extension baseline in BCVA to each post-baseline visit will be summarized descriptively by visit.

The number and percentage of patients with a loss of BCVA of 15 letters or more from extension baseline to each post baseline visit will be presented.

The extension baseline BCVA value is defined as the BCVA value at Day 1.

Last observation carried forward (LOCF) will be used to impute missing BCVA values (see Section 9.4.3 for further details).

BCVA over 96 weeks in the core study, for the same set of patients included in the extension safety set, will be displayed graphically alongside BCVA over 24 weeks for patients in the extension safety set.

q12 treatment status at Week 20

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

The estimate for the proportion of patients with a positive q12 treatment status at Week 20 will be derived from Kaplan Meier time-to-event analyses for the event ‘first q8-need’ applying a ‘q8-need’ allocation in case of missing or confounded data attributable to lack of efficacy and/or lack of safety. Remark: Patients without any relevant valid disease activity assessment are considered censored at extension baseline.

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

- For the ‘duration of effect’ requirement patients will need to have the status of ‘q8 need = no’ at Week 16 and Week 20 unless the ‘q8 need = yes’ is confounded by reasons other than lack of efficacy and/or safety (see censoring details below).

- The requirement regarding 'sufficient efficacy and safety' will be addressed by considering patients – even without an explicit 'q8 need = yes' – as having a negative q12 status in case any of the following confounding factors is attributable to lack of efficacy and/or lack of safety of the study treatment (assessed based on a masked medical review): early treatment/study discontinuation, use of forbidden concomitant medications/procedures and/or other deviation from treatment schedule (e.g. due to a missed visit/treatment). The corresponding q8 need will be allocated to the next disease activity assessment visit at Week 20 following the occurrence of such a confounding factor.

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

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

Using number and percent of patients, q12 treatment status at Week 20 in the extension safety set will be displayed by q12 treatment status at Week 96 in the core study and core study treatment group (brolucizumab 6 mg, brolucizumab 3 mg).

Anti-drug antibodies [redacted]

The number and percent of patients according to their ADA status (ADA negative, ADA positive without boost, induced, boosted) will be presented.

The ADA tier pattern and shift table showing ADA titer at extension baseline relative to each post-baseline assessment, relative to the last visit and to any visit with most extreme increase in ADA titer will be presented.

Extension baseline is defined as the ADA measurement at Day 1.

[redacted]

Central Subfield Thickness

The change in CSFT from extension baseline to each post-baseline visit will be summarized descriptively by visit.

The extension baseline CSFT value is defined as the CSFT value at Day 1.

LOCF will be used to impute missing CSFT values (see Section 9.4.3 for further details).

CSFT over 96 weeks in the core study, for the same set of patients included in the extension safety set, will be displayed graphically alongside CSFT over 24 weeks for patients in the extension safety set.

Intraocular pressure

Pre-injection IOP values and post-injection IOP values will be summarized by visit. Change from extension baseline IOP values will also be summarized by visit.

The number and percentage of patients with an IOP > 30mmHg will be presented separately for pre- and post-injection by visit. In addition, the number and percentage of patients with IOP > 30 mmHg at any visit and at the last visit will be presented.

Vital signs

Vital signs will be summarized for each visit. Changes from extension baseline will be summarized by visit. The number and percentage of patients with clinically notable findings from extension baseline will be presented by visit.

Extension baseline is defined as the last measurement before the injection given at Day 1.

9.4.3 Handling of missing values/censoring/discontinuations

Missing BCVA data will be imputed using LOCF. Observed values from both scheduled and unscheduled visits will be used for the LOCF imputation. For patients with no post baseline value, no imputation will be performed.

The details regarding handling of missing/ confounded data within the time-to-event analysis for the 'first q8 need' are specified in Section 9.4.2.

Missing CSFT data will be imputed using LOCF. Observed values from both scheduled and unscheduled visits will be used for the LOCF imputation. For patients with no post baseline value, no imputation will be performed.

All other data will be analyzed as observed, i.e. without imputation of missing data.

9.4.4 Sensitivity analyses

Best-Corrected Visual Acuity

Analyses of the BCVA variables described in Section 9.4.2 will be performed using observed data.

Central Subfield Thickness

Analyses of the CSFT variables described in Section 9.4.2 will be performed using observed data.

9.5 Analysis of secondary variables

Not applicable

9.5.1 Efficacy variables

Not applicable

9.5.2 Safety variables

Not applicable

9.5.3 Resource utilization

Not applicable

9.5.4 Pharmacokinetics

Not applicable

9.5.5 DNA

Not applicable

9.5.6 Biomarkers

Not applicable

9.5.7 PK/PD

Not applicable

9.6 Analysis of exploratory variables

Not applicable

9.7 Interim analyses

An interim analysis might be conducted when 50 patients are treated with brolucizumab 6 mg for 6 months to support a brolucizumab Biologic License Application submission at the earliest possible time point, which is currently planned for end of 2018.

The interim analysis will be performed with an unmasking of specified individuals from the sponsor who are not involved in the direct conduct of the trial.

Treatment masking of individual subjects will remain intact for all subjects, Investigators and staff from the sponsor who have contact with subjects or investigators or those who are involved with the direct conduct of the study until the final database lock has occurred.

9.8 Sample size calculation

Approximately 75 to100 patients who completed study CRTH258A2301 are expected to be enrolled in this study. This sample size is not based on a power calculation and depends on the number of patients in the core study fulfilling the eligibility criteria of the extension study (see Section 4).

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

For trials using an Electronic Informed Consent system where a date/timestamp is automatically generated, the system-generated date/timestamp is sufficient; additional input of the date at the time of consent is not required by the patient.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to patients/subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this

study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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