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Novartis Research and Development

RTH258

Clinical Trial Protocol CRTH258A2307 / NCT04047472

A Twelve-Month, Randomized, Double-Masked, Multicenter, Phase III, Two-Arm Study Comparing the Efficacy and Safety of Brolucizumab 6 mg versus Aflibercept in Chinese Patients with Neovascular Age-Related Macular Degeneration (HOBBY)

Document type:	Amended Protocol Version
EUDRACT number:	N/A
Version number:	04 (Clean)
Clinical Trial Phase:	III
Release date:	14-Jun-2022

Clinical Trial Protocol Template version 1.0 dated 01-Dec-2017

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List of abbreviations

A/G	albumin/globulin
ADA	anti-drug antibodies
AE	adverse event
ALT	alanine transferase
AMD	age-related macular degeneration
ANOVA	analysis of variance
AR	analysis restriction
AST	aspartate transferase
AUC	area under the curve
BCVA	best-corrected visual acuity
BUN	blood urea nitrogen
CFR	Code of Federal Regulation
CI	confidence interval
Cmax	maximum concentration
CMO&PS	Chief Medical Office and Patient Safety
CNV	choroidal neovascularization
CO	country organization
COA	clinical outcomes assessment
COVID-19	Coronavirus disease 2019
CRC	Central Reading Center
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSFT	Central Subfield Thickness
CSFTns	Central Subfield Thickness-neurosensory retina
CSFTtot	Central Subfield Thickness Total
CSR	Clinical Study Report
CV	coefficient of variation
DAA	disease activity assessment
DAR	dose administration record
DMC	Data Monitoring Committee
EC	Ethics committee
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
eSAE	Electronic Serious Adverse Event
ESI	Event of Special Interest
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiography
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	gamma glutamyl transaminase
HRQL	health related quality of life

[redacted]

IB	Investigator's Brochure
[redacted]	[redacted]
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICF	Informed consent form
IEC	Independent Ethics Committee
IOI	Intraocular inflammation
IN	Investigator Notification
IOP	intraocular pressure
IP	investigational product
IRB	Institutional Review Board
IRC	intraretinal cysts
IRF	intraretinal fluid
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
IVT	intravitreal
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
LOCF	last observation carried forward
LPLV	Last Patient Last Visit
MedDRA	Medical dictionary for regulatory activities
MMRM	mixed model repeated measures
nAMD	neovascular age-related macular degeneration
NEI	national eye institute
NIH	National Institutes of Health
OCT	Optical Coherence Tomography
[redacted]	[redacted]
PD	protocol deviation
PK	pharmacokinetic(s)
PPS	per-protocol set
PRO	patient reported outcome
PT	preferred term
q12w	every 12 weeks
QMS	Quality Management System
QoL	quality of life
RAP	retinal angiomatous proliferation
RAS	randomized analysis set
RAO	Retinal artery occlusion
RBC	red blood cell(s)
RO	Retinal vascular occlusion
RoW	rest of world
RPE	retinal pigment epithelium
RV	Retinal vasculitis
SAE	serious adverse event
SAP	Statistical Analysis Plan
scFv	single-chain variable fragment

SD-OCT	Spectral Domain Optical Coherence Tomography
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
SOP	Standard Operating Procedure
SRF	subretinal fluid
SUN	Standardization uveitis nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reactions
ULQ	upper limit of quantification
US	United States
USM	Urgent Safety Measures
VEGF	vascular endothelial growth factor
VFQ-25	Visual Function Questionnaire-25
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit
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 subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study 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”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes the subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.

[redacted]

Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
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 occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

[redacted]

Amendment 4 (14-Jun-2022)

Amendment rationale

In the spirit of the bridging concept under ICH E5, and also based on the cumulative evidence on brolucizumab as of today (i.e., from the two successful global pivotal Phase III studies RTH258-C001 (HAWK) and RTH258-C002 (HARRIER)), the main purpose of this amendment is to adjust the alpha level from 0.05 to 0.1 to result in a sample size reduction from approximately 494 to 390 subjects.
In particular, data from the two global pivotal studies, RTH258-C001 (HAWK) and RTH258-C002 (HARRIER), have demonstrated an overall favorable benefit-risk profile of brolucizumab in the treatment of subjects with nAMD. A total of 687 subjects were treated with brolucizumab 6 mg and completed Week 48 for the two pivotal studies. Both studies confirmed the hypotheses of non-inferiority of brolucizumab 6 mg to aflibercept 2 mg for the primary endpoint, BCVA change from Baseline to Week 48, with a non-inferiority margin of 4 letters (1-sided significance level of 0.025). The least squares mean difference between the brolucizumab and aflibercept arms for RTH258-C001 (HAWK) and RTH258-C002 (HARRIER) studies was respectively −0.2 letters and –0.7 letters, with a lower limit of the 95% CI being −2.1 letters ($p < 0.0001$), and −2.4 letters ($p= 0.0001$). Intraocular inflammation (IOI), an AE of special interest, was observed from 5.3% and 2.7% of the subjects in the brolucizumab 6 mg arm in their study eyes up to Week 48, respectively in the RTH258-C001 (HAWK) and RTH258-C002 (HARRIER) studies.

To demonstrate consistency in efficacy among Chinese subjects with what was observed in the two global pivotal studies, a statistical design with an alpha level of 0.1 is considered sufficient, which resulted in a sample size of approximately 390 subjects. Moreover, the proposed sample size will also provide sufficient evidence for the safety evaluation. Assuming similar IOI rates as observed from RTH258-C001 (HAWK) and RTH258-C002 (HARRIER) studies, with approximately 195 subjects in the brolucizumab arm, there is a 99.6% and 85.4% probability respectively to observe at least 3 subjects that would experience IOI.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough (red font for deletions and red underlined for insertions).

Protocol sections changed in relation to this population reduction are:

- Protocol Summary: Population sample size and significance level alpha for data analysis are updated.
- Section 5 Population: Population sample size updated.
- Section 12.4.2 Statistical model, hypothesis, and method of analysis: Significance level alpha is updated for statistical hypotheses testing.
- Section 12.5.1 Efficacy and/or Pharmacodynamic endpoint(s): Confidence interval level updated for secondary efficacy endpoints.

[redacted]

- Section 12.8.1 Primary endpoint(s): Sample size calculation is updated with significance level alpha = 0.1.

Other minor clarifications and corrections were made where applicable.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 3 (14-Jan-2022)

Amendment rationale

Amendment version 2 did not carry through some of the changes that had already been implemented in Amendment version 1 in Section 12 Data analysis and statistical methods of the protocol. The purpose of this amendment is to reinstate these changes from Amendment version 1.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough (red font for deletions and red underlined for insertions).

Protocol sections changed include Section 12.4.2, Table 12-1, and Section 12.4.4, in order to reflect the changes amended in protocol version 1.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval, according to local regulations, prior to implementation.

Amendment 2（14-Oct-2021)

Amendment rationale

The main purpose of this amendment is to implement the Urgent Safety Measures (USM) described in the 10-Aug-2021 Dear Investigator Letter (DIL) into the study protocol. The USM were implemented for ongoing studies not achieving Last Patient Last Visit (LPLV) by 11-Aug-2021 and in response to the identification of a causal immune-mediated mechanism of the previously identified risk of retinal vasculitis (RV), and/or retinal vascular occlusion (RO), typically in the presence of intraocular inflammation (IOI) indicating a requirement to discontinue treatment with brolucizumab (RTH258) in patients who develop events of RV and/or RO.

This amendment also includes information on gender imbalance on IOI following brolucizumab treatment and recommendations on the time window for a study subject to receive the COVID-19 vaccine. Some other administrative changes have also been incorporated.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strikethrough (red font for deletions and red underlined for insertions).

Protocol sections changed in relation to this emerging safety measure are:

- Section 1.1 Background: Information added to describe Urgent Safety Measures
- Section 4.5 Risk and benefits: Information added to describe Urgent Safety Measures and additional information on gender imbalance on IOI following brolucizumab treatment
- Section 8.4.3 Ophthalmic examination: Requirement of treatment discontinuation was added if subject developed RV and/or RO.

Other changes incorporated in this amendment

- Table 2-1 Objectives and related endpoints: [redacted]
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action: added recommendations on the time window for a study subject to receive the COVID-19 vaccine.
- Section 6.7.2 Instruction for administering study treatment: Requirement of treatment discontinuation was added if subject developed RV and/or RO, in both arms.
- Table 8-1 Assessment Schedule: footnote was added to clarify that PK parameters will be measured by using blood collection for ADA analysis at visit 6 since PK and ADA testing are both required at this visit in the study.
- Section 8.5.2 Pharmacokinetics: to make consistent with the following wordings (approximately 12 subjects per treatment arm to maintain masking).

[redacted]

- Section 8.5.3 Other Assessments: To clarify that PK parameters would be determined using the blood collected for ADA analysis at visit 6.
- Section 9.1.1 Discontinuation of study treatment: Changes were made as follows:

  Subject develops a retinal vasculitis and/or a retinal vascular occlusion event
- Section 9.1.2 Withdrawal of informed consent /Opposition to use data/biological samples: To further clarify the definition of withdrawal of informed consent.
- [redacted]
- Other minor clarifications and corrections were made where applicable.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 1 (08-Jun-2020)

Amendment rationale

The main purpose of this amendment is to provide clarification and guidance on safety assessments in accordance to the urgent safety measure regarding the post-marketing reports with brolucizumab (Beovu®) in the treatment of nAMD, which were identified as retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, that may result in severe vision loss. In addition, the amendment includes the modifications due to COVID-19 pandemic.

Changes to the protocol

Protocol sections changed in relation to this emerging safety issue are:

- Section 1.1 Background: Information was added to describe new safety signal from post-marketing case reports.
- Section 6.7.2 Instructions for prescribing and taking study treatment: Additional guidance was added to this section emphasizing that if any sign of intraocular inflammation is present, an IVT injection must not be performed and patients should be treated for IOI according to clinical practice.
- Additional examination and assessments included to fully characterize cases of intraocular inflammation were made in the following sections:
- Table 8-1 Assessment schedule
- Section 8.3.3 Color fundus photography and fluorescein angiography
- Section 8.4.3 Ophthalmic Examination
- Section 8.4.5 Other safety evaluations

Changes were incorporated to address the COVID-19 pandemic in the following sections:

- Section 7 Informed Consent Procedures
- Section 8 Visit Schedule and Assessments
- Section 8.4 Safety
- Section 8.4.1 Laboratory evaluations
- Section 12 Data analysis and statistical methods

Other changes incorporated in this amendment:

- Section 1.1 Background: Updated HAWK/ HARRIER study status.
- Section 6.4 Treatment masking: Language was added to clarify unmasked investigator/site personnel must not be switched to a masked role at any time after randomization.
- Table 8-1 Assessment schedule: delete the row of visit number and related footnote since it is only for internal use. Update the superscript and number of footnote.
- Section 8.2 Subject demographics/other baseline characteristics: Removed ethnicity since it was not collected in the study.
- Section 8.3.3 Color fundus photography and fluorescein angiography [redacted]: Change the previous routine evaluation period of image before screening visit from 3 days to 14 days to be consistent with other studies in RTH program.

[redacted]

- Section 8.4.3 Ophthalmic examination: Expanded IOP measurement to non-contact tonometer to follow the local clinical practice. Clarification on the timing for post-injection IOP measurement.
- Section 8.5.3 Other assessments
- Section 10.1.3 SAE Reporting: Clarification of the SAE reporting period.
- Section 12 Analysis sets and statistical methods: Language was adapted to clarify primary and supplementary estimands and analyses based on estimands
- Section 12.2 Subject demographics and other baseline characteristics: Removed ethnicity analysis to align with change in section 8.2.
- Section 15 References: References were added regarding grading systems of anterior chamber cells and flare, and vitreous cells and haze.

Updated the List of Abbreviations and Glossary of terms

Other minor clarifications were made where applicable. Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

This amendment is required for patient safety (i.e. necessary to eliminate immediate hazards to the trial subjects ICH GCP 3.3.8). Therefore it will be implemented prior to IRB/IEC approval, but will be sent for approval as well.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CRTH258A2307
Full Title	A Twelve-Month, Randomized, Double-Masked, Multicenter, Phase III, Two-Arm Study Comparing the Efficacy and Safety of Brolucizumab 6 mg versus Aflibercept in Chinese Patients with Neovascular Age-Related Macular Degeneration (HOBBY)
Brief title	Study of efficacy and safety of brolucizumab vs. aflibercept in Chinese patients with Neovascular Age-Related Macular Degeneration
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to evaluate the efficacy and safety of brolucizumab in treatment of Chinese patients with Neovascular Age-Related Macular Degeneration (nAMD)
Primary Objective(s)	To demonstrate that brolucizumab 6 mg is not inferior to aflibercept 2 mg with respect to the change in Best Corrected Visual Acuity (BCVA) after 48 weeks of treatment
Secondary Objectives	To assess the efficacy and the ocular and systemic safety of brolucizumab: • To estimate the proportion of q12w subjects (1 injection every 12 weeks) up to Week 48 in the brolucizumab 6 mg treatment arm • To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment up to Week 48 in the brolucizumab 6 mg treatment arm • To evaluate the efficacy of brolucizumab 6 mg relative to aflibercept 2 mg over the time period up to Week 48 by assessing changes in BCVA • To evaluate the efficacy of brolucizumab 6 mg relative to aflibercept 2 mg over the time period up to Week 48 by assessing changes in anatomical parameters of disease activity • To evaluate the efficacy of brolucizumab 6 mg relative to aflibercept 2 mg at the end of the matched treatment phase • To assess the safety and tolerability of brolucizumab 6 mg relative to aflibercept 2 mg • To assess visual function-related subject reported outcomes following treatment with brolucizumab 6 mg relative to aflibercept 2 mg • To assess immunogenicity of brolucizumab 6 mg • To assess systemic PK of brolucizumab at 6 mg following a single intravitreal (IVT) injection
Study design	In this twelve-month, randomized, double-masked, multicenter, active controlled study, consenting patients will participate in a screening period, lasting up to 14 days. Eligible patients will be randomized in a 1:1 ratio to one of the two treatment arms: • Brolucizumab 6 mg: 3 x q4w followed by q12w/q8w up to Week 40 or Week 44, depending on disease activity status. • Aflibercept 2 mg: 3 x q4w followed by q8w up to Week 40
Population	Approximately 390 randomized Chinese patients ≥ 50 years of age with untreated active choroidal neovascularization (CNV) secondary to Age-Related Macular Degeneration (AMD) in the study eye
Key Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. 2. Male or female Chinese patient ≥ 50 years of age at the time of screening. Study Eye 1. Active choroidal neovascularization (CNV) lesions secondary to AMD that affect the central subfield (including retinal angiomatous proliferation (RAP) lesions with a CNV component) in the study eye at screening

[redacted]

	2. Total area of CNV (including both classic and occult components) must comprise > 50% of the total lesion area in the study eye at screening and confirmed by the Central Reading Center (CRC). 3. Intra and/or subretinal fluid affecting the central subfield of the study eye at screening and confirmed by the CRC. 4. BCVA between 78 and 23 letters, inclusive, in the study eye at screening and Baseline using Early Treatment Diabetic Retinopathy Study (ETDRS) testing.
Key Exclusion criteria	1. Any active intraocular or periocular infection or active intraocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis, uveitis) in study eye at Baseline. 2. Central subfield of the study eye affected by fibrosis or geographic atrophy assessed by color fundus photography at screening and confirmed by the CRC. 3. Total area of fibrosis ≥ 50% of the total lesion at screening 4. Subretinal blood affecting the foveal center point and/or ≥50% of the lesion at screening 5. Previous treatment with any approved or investigational drugs for neovascular AMD in the study eye (other than vitamin supplements). 6. Retinal pigment epithelium (RPE) rip/tear in the study eye at screening. 7. Current vitreous hemorrhage or history of vitreous hemorrhage in the study eye within 4 weeks prior to Baseline.
Study treatment	• Brolucizumab 6 mg • Aflibercept 2 mg
Efficacy assessments	• Visual Acuity • Optical Coherence Tomography (OCT) • Color fundus photography and fluorescein angiography (FA) [redacted]
Pharmacokinetic assessments	• Systemic brolucizumab exposure
Key safety assessments	• Adverse Events, including Adverse Events of special interest • Vital Signs • Blood chemistry/hematology/urinalysis • Standard ophthalmic examinations
Other assessments	• Visual Function Questionnaire-25 (VFQ-25) • Anti-drug antibody (ADA) status of brolucizumab
Data analysis	**Primary analysis data set:** The primary data set for all efficacy analyses is the full analysis set (FAS) with missing values imputed by last observation carried forward (LOCF). The FAS comprises all subjects to whom study treatment has been assigned by randomization and who receive at least one IVT injection of the study treatment. **Primary and key secondary endpoints:** The primary efficacy endpoint is the change from Baseline in BCVA at Week 48. The first key secondary endpoint is average change in BCVA from Baseline over the period Week 36 through Week 48. **Statistical Hypotheses and testing strategy:** The statistical hypothesis for the primary endpoint and first key secondary endpoint is non-inferiority of brolucizumab 6 mg to aflibercept 2 mg within a margin of 4 letters. The following 2 hypotheses will be tested in the pre-specified hierarchical sequence according to their numbering (HAn, n = 1, 2). Consequently, confirmatory testing of the second hypothesis requires rejection of the first null hypothesis. In this setting, each hypothesis will be assessed at a one-sided significance level of 0.05, while keeping the global type I error rate at 0.05. The following noninferiority hypotheses are related to a noninferiority margin of 4 letters.

[redacted]

	48 = Week 48, 36-48 = Week 36 through 48, R= brolucizumab 6 mg, A= aflibercept 2 mg H_{01}: $\mu_{48R} - \mu_{48A} \leq -4$ letters vs H_{A1}: $\mu_{48R} - \mu_{48A} > -4$ letters μ_{48R} and μ_{48A} being the corresponding unknown true mean BCVA changes from Baseline to Week 48. H_{02}: $\mu_{36\text{-}48R} - \mu_{36\text{-}48A} \leq -4$ letters vs H_{A2}: $\mu_{36\text{-}48R} - \mu_{36\text{-}48A} > -4$ letters $\mu_{36\text{-}48R}$ and $\mu_{36\text{-}48A}$ being the corresponding unknown true mean values for the average change in BCVA from Baseline over the period Week 36 through 48. **Primary statistical method:** For the test of non-inferiority, a two-sided 90% CI for the treatment difference will be derived from an analysis of variance (ANOVA) model with treatment, Baseline BCVA categories (≤ 55, 56-70, ≥ 71 letters) and age categories (< 75, ≥ 75 years) as factors. In order to demonstrate non-inferiority, the lower limit of the two-sided 90% CI for the treatment difference (brolucizumab 6 mg – aflibercept 2 mg) must be greater than -4 letters. **Sample size justification:** In the spirit of bridging concept under ICH E5, A sample size of 175 subjects per treatment arm is sufficient to demonstrate noninferiority (margin = 4 letters) of brolucizumab 6 mg versus aflibercept 2 mg with respect to the BCVA change from Baseline to Week 48 at a one-sided alpha level of 0.05 with a power of approximately 80% assuming equal efficacy and a common standard deviation of 15 letters. A power of at least 80% can be expected for the first key secondary endpoint assuming that averaging BCVA change from Baseline over the 4 time points will not lead to an increase in the standard deviation. To account for a drop-out rate of 10%, a total of 195 subjects will be randomized per treatment arm.
Key words	Neovascular Age-related Macular Degeneration (AMD), intravitreal injection, brolucizumab, aflibercept, double-masked

[redacted]

1 Introduction

1.1 Background

Age-related macular degeneration (AMD) is the leading cause of severe vision loss affecting 10%-13% of people over the age of 65 in North America, Europe, and Australia (Smith et al 2001, Rein et al 2009, Kawasaki et al 2010).

There are few data on the epidemiology of AMD in the Asian population. In a Shihpai Eye Study (Hsu et al 2004), a population-based cross-sectional study of an elderly Chinese population 65 years or older in Taiwan, AMD was the cause of visual impairment in 10.4% of the subjects. In the epidemiological study in Shanghai China, it was reported that the prevalence of AMD (dry and wet combination) was 15.5% of the overall population that were more than 50 years old (Li X 2013). The prospective Hisayama study in a Japanese population aged 50 years or older reported for AMD prevalence of 19.5% in men and of 14.9% in women (Miyazaki et al 2003). Considering an aging population and socioeconomic development, it is expected that the incidence of visual impairment due to AMD will increase over time in China (Wong et al 2008).

AMD is classified into 2 clinical subtypes: the non-neovascular (atrophic) or dry form and the neovascular (exudative) or wet form (Ferris 1983, Lim et al 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 et al 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 and Del Priore 2007, Shah and Del Priore 2009). Without treatment, most affected eyes will have poor central vision (20/200) within 12 months (Blinder et al 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 et al 1991, Wong et al 2008).

Anti-VEGFs and unmet medical need in treatment of nAMD VEGF has been shown to be elevated in patients with neovascular AMD (nAMD), and is thought to play a key role in the neovascularization process (Spilsbury et al 2000). The use of intravitreal (IVT) pharmacotherapy targeting VEGF has significantly improved visual outcomes in patients with neovascular AMD (Bloch et al 2012, Campbell et al 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. However, the patient monitoring and treatment burden remain high with approved anti-VEGF therapies.

Currently, three anti-VEGFs are approved for treatment of nAMD in China: ranibizumab (Lucentis®), conbercept (Lumitin®) and aflibercept (Eylea®). The Chinese prescribing information recommends a loading phase for all anti-VEGFs in nAMD, followed by less frequent injections in a comparable range as in other countries. Lucentis® is dosed monthly for the first three months, followed by 4 – 5 injections per year or by injections every 3 months, but with reduced efficacy compared to monthly dosing. Eylea® is dosed monthly for the first three months followed by injections every 2 months (8 weeks), and Lumitin® is dosed monthly

[redacted]

for the first three months followed by injections every 3 months, while both efficacies compared to Lucentis® have not been established.

Physicians have responded to the treatment burden in nAMD by exploring different regimens with fewer injections (Gupta et al 2011). In the real-world setting, patients with nAMD may not achieve the best possible long-term outcomes (Tufail et al 2014, Holz et al 2014, Chong 2016), as vision continues to decline despite anti-VEGF treatment often due to the underutilization of treatment and monitoring (Holz et al 2015). Some patients undergo treatment fatigue with anti-VEGF therapies and choose to discontinue treatment. (Boulanger-Scemama et al 2015). This can result in recurrent disease and permanent vision loss (Essex et al 2016). Therefore, unmet medical needs for effective and more durable anti-VEGF therapies still exist for patients with nAMD (Freund et al 2013).

Brolucizumab development program in nAMD Brolucizumab (RTH258, formerly ESBA1008) is a humanized single-chain Fv (scFv) antibody fragment inhibitor of vascular endothelial growth factor A 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 smaller molecular size of the scFv delivers a higher molar dose, which prolongs the therapeutic effect and enables better tissue penetration at the retina, compared to whole antibodies and larger antibody fragments. 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 subjects 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, SEE),
- 56-week multiple dose study of brolucizumab 6 mg versus aflibercept 2 mg (Alcon protocol C-12-006, OSPREY),
- 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, OWL),
- 3 dose study of brolucizumab at 6mg or 3mg in patients of Japanese and non-Japanese ancestry (Alcon protocol RTH258-E003 also referred to as CRTH258A2201, SHRIKE).

Two pivotal, two-year, randomized, double-masked, multicenter phase III studies of brolucizumab were completed in patients with nAMD: RTH258-C001 (HAWK) and RTH258-C002 (HARRIER). The primary objective of both studies was to demonstrate noninferiority of brolucizumab to aflibercept. Analysis of data up to Week 48 demonstrated noninferiority of brolucizumab 3 mg and 6 mg versus aflibercept in mean change in BCVA from Baseline to Week 48. A majority of subjects, 56% (HAWK) and 51% (HARRIER), were maintained exclusively on a q12w interval following the loading phase through Week 48. Brolucizumab was generally well tolerated with overall adverse event rates comparable to aflibercept.

In general, 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.

[redacted]

Since the initial marketing authorization approval in October 2019 for the treatment of nAMD, adverse events of retinal vasculitis and/or retinal vascular occlusion, that may result in severe vision loss and typically in the presence of intraocular inflammation, have been reported from post-marketing experience with brolucizumab (Beovu®). Results of the mechanistic study BASICHR0049 on blood samples from nAMD patients exposed to brolucizumab and having subsequently developed retinal vasculitis and/or retinal vascular occlusion, taken together with accumulated data from HAWK, HARRIER and CRTH258AUS04 (MERLIN), regarding the association of treatment-emergent immunogenicity and IOI, indicate a causal link between the treatment-emergent immune reaction against brolucizumab and the brolucizumab-related retinal vasculitis and/or retinal vascular occlusion, typically in the presence of IOI. Considering the incidence of these events is uncommon, the overall risk/benefit assessment remains positive.

Please refer to the Brolucizumab Investigator's Brochure (IB) for further details.

1.2 Purpose

The purpose of the study is to evaluate the efficacy and safety of brolucizumab 6 mg versus aflibercept 2 mg in Chinese patients with nAMD.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that brolucizumab 6 mg is not inferior to aflibercept 2 mg with respect to the change in BCVA after 48 weeks of treatment	• Change in BCVA from Baseline to Week 48 • Average change in BCVA from Baseline over the period Week 36 to Week 48
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To estimate the proportion of q12w subjects (1 injection every 12 weeks) up to Week 48 in the brolucizumab 6 mg treatment arm	• q12w treatment status at Week 48 (for subjects randomized to brolucizumab 6 mg only)
• To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment up to Week 48 in the brolucizumab 6 mg treatment arm	• q12w treatment status at Week 48 within the subjects with no q8w need during the first q12w cycle (Week 16 and Week 20) (for subjects randomized to brolucizumab 6 mg only)
• To evaluate the efficacy of brolucizumab 6 mg relative to aflibercept 2 mg over the time period up to Week 48 by assessing changes in BCVA	• Change in BCVA from Baseline to each postbaseline visit • Average change in BCVA from Baseline over the period Week 4 to Week 48 • Average change in BCVA from Baseline over the period Week 12 to Week 48 • Gain in BCVA of 15/10/5 letters or more from Baseline at each postbaseline visit • Number and percentage of subjects with BCVA of 73 letters or more at each visit • Loss in BCVA of 15/10/5 letters or more from Baseline at each postbaseline visit
• To evaluate the efficacy of brolucizumab 6 mg relative to aflibercept 2 mg over the time period up to Week 48 by assessing changes in anatomical parameters of disease activity	• Change in CSFTtot from Baseline to each postbaseline visit • Average change in CSFTtot from Baseline over the period Week 36 through Week 48 • Average change in CSFTtot from Baseline over the period Week 4 to Week 48

[redacted]

Objective(s)	Endpoint(s)
	• Change in CSFTns from Baseline to each postbaseline visit • Change in area of CNV lesion from Baseline at Weeks 12 and 48 • Presence of subretinal and/or intraretinal fluid (central subfield) at each postbaseline visit (and specifically Week 16 and Week 48) • Number of visits with simultaneous absence of subretinal and intraretinal fluid (central subfield) during Week 36 to Week 48 • Presence of subretinal fluid (central subfield) at each postbaseline visit • Presence of intraretinal fluid (central subfield) at each postbaseline visit • Presence of sub RPE fluid (central subfield) at each postbaseline visit
• To evaluate the efficacy of brolucizumab 6 mg relative to aflibercept 2 mg at the end of the matched treatment phase	• Change in CSFTtot from Baseline at Week 16 • Presence of subretinal and/or intraretinal fluid (central subfield) at Week 16 • q8w treatment need identified at Week 16
• To assess the safety and tolerability of brolucizumab 6 mg relative to aflibercept 2 mg	• Incidence and characteristics of treatment-emergent adverse events • Treatment-emergent changes in ocular and systemic parameters • Presence of fibrosis from color fundus photography by assessment visit
• To assess visual function-related subject reported outcomes following treatment with brolucizumab 6 mg relative to aflibercept 2 mg	• Change in subject reported outcomes (VFQ-25) total and subscale scores from Baseline to Weeks 24 and 48
• To assess immunogenicity of brolucizumab 6 mg	• ADA status at Baseline (enrollment), Weeks 4, 12, 24, 36, and 48 (End of Study)
• To assess systemic PK of brolucizumab at 6 mg following a single IVT injection	• PK parameters after first brolucizumab 6 mg dose in a subset of subjects
[redacted]	

3 Study design

This is a randomized, double-masked, multicenter, parallel-group, active-controlled study. The study includes 14 scheduled visits over 48 weeks. A screening period of 2 weeks will be used to assess eligibility.

[redacted]

After confirmation of eligibility at Baseline, patients will be randomized in a 1:1 ratio to one of the two treatment arms:

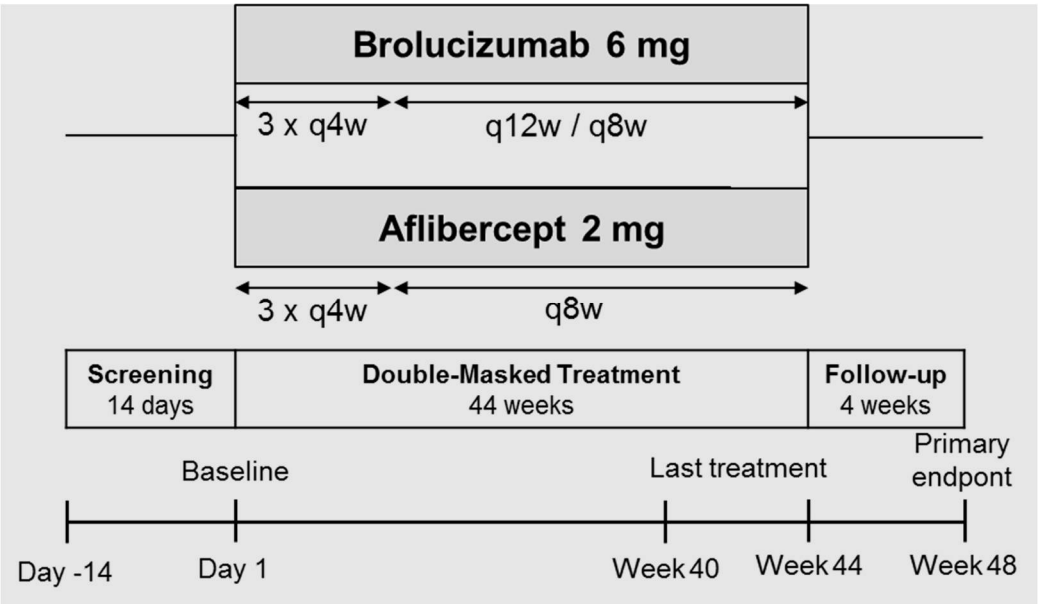
- Brolucizumab 6 mg: three monthly intravitreal injections of brolucizumab 6 mg in the loading treatment period (q4w regimen) up to Week 8 followed by injections every 12 weeks (q12w regimen) or 8 weeks (q8w regimen) up to Week 40 or Week 44, depending on disease activity status.
- Aflibercept 2 mg: three monthly intravitreal injections of aflibercept 2 mg in the loading treatment period (q4w regimen) up to Week 8 followed by injections every 8 weeks (q8w regimen) up to Week 40.

Only one eye fulfilling all eligibility criteria will be selected/ treated and will be defined as the study eye.

There are no stratification factors in this study.

For an overview of the study design please see Figure 3-1 below:

Figure 3-1 Study design



q4w - injection every 4 weeks; q8w - injection every 8 weeks; q12w - injection every 12 weeks

4 Rationale

4.1 Rationale for study design

This study is designed as a randomized, multi-center, double-masked, 2 arm, active controlled, prospective study to demonstrate the safety and efficacy of brolucizumab 6 mg against the active control, aflibercept 2 mg, used per approved label in China. Since the treatment schedule is different between arms, to ensure masking, the following will apply:

[redacted]

- subjects will receive active or sham injection at each protocol visit except Week 12 and Week 48 visits (no scheduled treatment for any arm),
- disease activity assessment (DAA) will be performed for both arms at protocol specified visit,
- to fulfill the double-masking requirement, the investigational site will have masked and unmasked staff.

Non-inferiority testing related to the primary efficacy parameter Best-corrected visual acuity (BCVA) will be based on a margin of 4 letters. This non-inferiority margin provides assurance that any proof of non-inferiority only occurs if the observed treatment differences are of no clinical relevance.

The patient population will be described in more detail in Section 5.

4.2 Rationale for dose/regimen and duration of treatment

The dose and regimen for brolucizumab are based on:

- The performed analysis of data up to Week 48 from the two phase III brolucizumab studies (HAWK and HARRIER) in nAMD, brolucizumab 6 mg and 3 mg doses showed comparable efficacy and safety profiles to aflibercept 2 mg.
- The numerical differences between the 3 mg and 6 mg dose seen in the functional and anatomical endpoints, in the proportion of subjects on a q12w dosing regimen and in the control of disease activity consistently favor the 6 mg dose. Overall, the safety of brolucizumab 6 mg was comparable to the 3mg dose. Hence, brolucizumab 6 mg dose will be used in this study.

Aflibercept will be administered as per the approved label in China.

Route of administration is intravitreal injection as for all anti-VEGF treatments currently approved for treatment of nAMD.

Study duration of 48 weeks is deemed sufficient to assess efficacy and safety of brolucizumab 6 mg administered at the target q12w dosing regimen. The 2 year data of the aflibercept studies (View 1 and View 2) showed that the mean BCVA change from Baseline reaches a plateau during the first year of treatment, which to a large degree is sustained during the second year (Schmidt-Erfurth et al 2014). Similar results were observed in the ranibizumab study (Li et al 2016) with Chinese population that BCVA improvement in the first year was maintained during the second year. Also the brolucizumab Phase III studies (HAWK and HARRIER) used the time point of 48 weeks for the primary endpoint and also showed that BCVA reached a plateau during the first year of treatment.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Aflibercept 2 mg is an established standard of care anti-VEGF treatment for nAMD in US and EU, which has been recently approved in China in May 2018.

Aflibercept has been chosen as a comparator in two recently completed global brolucizumab Phase III studies RTH258-C001 (HAWK) and RTH258-C002 (HARRIER) due to the consistency of the approved dose and posology of aflibercept in most countries worldwide.

[redacted]

Using the same comparator as in the global pivotal studies will support the comparison of the results between China and global study populations.

Due to the well-established efficacy of anti-VEGF treatments in the indication of nAMD, an internal validation of this study via a placebo arm is ethically not acceptable.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, and periodic review of safety data by an independent program level data monitoring committee (DMC).

Women of childbearing potential and sexually active males 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 requirements outlined in the exclusion criteria. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

Brolucizumab is an inhibitor of VEGF with a mechanism of action similar to ranibizumab or aflibercept with a smaller molecular size (26 kDa and 48 kDa or 115 kDa, respectively). Ranibizumab and aflibercept (both approved inhibitors of VEGF-A) have consistently demonstrated efficacy in VEGF-driven retinal pathologies, including nAMD, with benefits outweighing the risks. Assuming a corresponding class-effect, it is justified to expect that brolucizumab (having the same MoA as ranibizumab and aflibercept) will likewise be efficacious and have a similar safety profile in the nAMD indication. In both Phase III studies (HAWK, HARRIER) in nAMD, brolucizumab demonstrated non-inferiority to aflibercept in mean change in BCVA from Baseline to Week 48. These results were achieved while a majority of patients on brolucizumab 6 mg – 56% in HAWK and 51% in HARRIER – were maintained on a q12w dosing interval following the loading phase through Week 48, i.e. with a reduced treatment frequency compared to aflibercept. Brolucizumab safety was comparable to aflibercept, with the overall incidence of adverse events balanced across all treatment groups in both studies. Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of IOI has been reported following brolucizumab injection. These immune mediated adverse events may occur following the first intravitreal injection. Discontinuation of study treatment is required in subjects who develop these events. In addition, subjects who experience IOI may be at risk of developing retinal vasculitis and/or retinal vascular occlusion and should be closely monitored.

Based on clinical studies, IOI related adverse events, including retinal vasculitis and retinal vascular occlusion, were reported more frequently in female patients treated with brolucizumab than male patients (e.g. 5.3% females vs. 3.2% males in HAWK and HARRIER, Novartis data on file).

Overall, brolucizumab was well tolerated in clinical studies with nAMD subjects when treatment interval is not less than every 8 weeks after the first 3 monthly initial doses (loading phase). The risk/benefit assessment for brolucizumab remains positive.

[redacted]

Further details of the known and potential risks and benefits associated with brolucizumab are presented in the IB.

5 Population

The study population will consist of male and female Chinese patients (≥50 years of age) with untreated active CNV secondary to AMD in the study eye. Approximately 488 patients will be screened (20% screening failure rate expected) and approximately 390 patients will be randomized (195 per arm) in approximately 30 sites in China.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male or female Chinese patient ≥ 50 years of age at the time of screening.
3. Active choroidal neovascularization (CNV) lesions secondary to AMD that affect the central subfield (including retinal angiomatous proliferation [RAP] lesions with a CNV component) in the study eye at screening and confirmed by the Central Reading Center (CRC).
4. Total area of CNV (including both classic and occult components) must comprise > 50% of the total lesion area in the study eye at screening and confirmed by the CRC.
5. Intra and/or subretinal fluid affecting the central subfield of the study eye at screening and confirmed by the CRC.
6. BCVA between 78 and 23 letters, inclusive, in the study eye at screening and Baseline using Early Treatment Diabetic Retinopathy Study (ETDRS) testing.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Any active intraocular or periocular infection or active intraocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis, uveitis) in study eye at Baseline.
2. Central subfield of the study eye affected by fibrosis or geographic atrophy assessed by color fundus photography at screening and confirmed by the CRC.
3. Total area of fibrosis ≥ 50% of the total lesion in the study eye at screening and confirmed by the CRC.
4. Subretinal blood affecting the foveal center point and/or ≥50% of the lesion of the study eye at screening and confirmed by the CRC.
5. Previous treatment with any approved or investigational drugs for neovascular AMD in the study eye (other than vitamin supplements).
6. Any history or evidence of a concurrent intraocular condition in the study eye, including retinal diseases other than neovascular AMD, that, in the judgment of the Investigator, could require medical or surgical intervention during the course of the study to prevent or treat visual loss that might result from that condition, or that limits the potential to gain visual acuity upon treatment with the investigational product (IP).
7. Retinal pigment epithelium (RPE) rip/tear in the study eye at screening.

[redacted]

8. Current vitreous hemorrhage or history of vitreous hemorrhage in the study eye within 4 weeks prior to Baseline.
9. History or evidence of the following in the study eye:
   - intraocular or refractive surgery within the 90 day period prior to Baseline
   - previous penetrating keratoplasty or vitrectomy
   - previous panretinal photocoagulation
   - previous submacular surgery, other surgical intervention or laser treatment for AMD
10. Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication or according to Investigator's judgment at screening and Baseline.
11. Aphakia and/or absence of the posterior capsule in the study eye at screening.
12. Use of dexamethasone intravitreal implant (Ozurdex) or fluocinolone acetonide intravitreal implant (Iluvien) in study eye at any time. Intra- or periocular use of corticosteroids in the study eye during the 6 month period prior to Baseline.
13. Any history of uveitis in either eye.
14. Previous treatment with any anti-VEGF drugs in the study eye.
15. Use of systemic corticosteroids for 30 or more consecutive days within the 90 days prior to Baseline, with the exception of low stable doses of corticosteroids (defined as ≤ 10 mg prednisolone or equivalent dose used for 90 days or more prior to Baseline). Inhaled, nasal or dermal steroids are permitted.
16. Previous therapeutic radiation near the region of the study eye.
17. Treatment with any anti-VEGF within the 4 week period prior to Baseline in the nonstudy eye.
18. History of a medical condition (disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding) that, in the judgment of the Investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product.
19. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
20. Pregnant or nursing (lactating) women.
21. 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 months after stopping of investigational medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - 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
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system

(IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception
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.
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.

22. Use of other investigational drugs within 5 half-lives of enrollment, or [within 30 days /until the expected pharmacodynamic effect has returned to Baseline], whichever is longer.
23. Systemic anti-VEGF therapy during the 3 month period prior to Baseline.
24. Stroke or myocardial infarction in the 6 month period prior to Baseline.
25. Uncontrolled blood pressure defined as a systolic value ≥ 160 mmHg or diastolic value ≥ 100 mmHg at screening and Baseline.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

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

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply type	Sponsor (global or local)
Brolucizumab 6 mg	Sterile solution for injection	Intravitreal injection	Open label supply in Sterile glass vial. Masking at the clinical site by unmasked site personnel	Sponsor global
Aflibercept 2 mg	Sterile solution for injection	Intravitreal injection	Open label supply in Sterile glass vial. Masking at the clinical site by unmasked site personnel	Sponsor global

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). 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.

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

[redacted]

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.

Sham injections refer to an imitation of an intravitreal injection procedure using an empty sterile syringe without a needle. There will be no sham vials.

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.

6.1.2 Additional study treatments

No additional treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Patients will be assigned at Baseline visit to one of the following two treatment arms in 1:1 ratio:

- Brolucizumab 6 mg: 3 x q4w up to Week 8 followed by q12w / q8w up to Week 40 or Week 44, depending on disease activity status.
- Aflibercept 2 mg: 3 x q4w up to Week 8 followed by q8w up to Week 40.

6.1.4 Treatment duration

The planned study duration is 48 weeks with the last aflibercept treatment at Week 40 and the last brolucizumab treatment at Week 40 or Week 44, depending on dosing regimen (q8w or q12w, respectively). Subjects may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the subject. For subjects who in the opinion of the investigator are still deriving clinical benefit from the study drug, every effort will be made to continue provision of study treatment.

6.2 Other treatment(s)

Not applicable.

[redacted]

6.2.1 Concomitant therapy

The investigator must instruct the patient to notify the study site about any new medications he/she takes after signing the study informed consent. 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 electronic case report form (eCRF) page.

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 randomizing a patient or allowing a new medication to be started. If the subject is already enrolled, contact Novartis/sponsor to determine if the subject should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Non-investigational treatment for fellow eye is permitted 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 Case Report/Record Form (CRF).

Administration of topical ocular corticosteroids are permissible in the study eye during the course of the study. If the subject is planning to receive a COVID-19 vaccine that is authorized by local regulation, it is recommended to receive the vaccine at least 7 days before or after the study treatment visit including Baseline (Day 1) visit.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed after screening.

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Study eye		
Anti-VEGF therapy other than study medication	Any time	Discontinue study treatment
Intra- or periocular corticosteroids (except if needed as short term treatment of AE)	Any time	Discontinue study treatment (except if for treatment of AE)
Any Laser treatment for nAMD	Any time	Discontinue study treatment
Any other investigational drug, biologic or device	Any time	Discontinue study treatment
Fellow eye		
Unapproved or 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

6.2.3 Rescue medication

Subjects who received rescue therapy (standard of care) per investigator's discretion will be required to discontinue with the study treatment but may continue with the study follow-up procedures.

[redacted]

Use of rescue medication (standard of care) in the study eye will be documented in the source documents and recorded in the eCRF.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (4 digit number for Center No. as assigned by Novartis to the investigative site) with a sequential subject number (3 digit number) suffixed to it, so that each subject is numbered uniquely across the entire database.

Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available in electronic data capture (EDC) system. The investigator or her/his staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information for the patient to register them into the IRT. Once assigned to a patient, the patient number will not be reused for another patient. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography eCRF should be completed. Patients who have been screen failures but are re-screened (see Section 8.1) will be assigned a new Subject No.

6.3.2 Treatment assignment, randomization

At Baseline visit, all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms, in a ratio of 1:1. There are no stratification factors in this study.

The investigator or her/his delegate will contact the IRT, after it was confirmed that the patient fulfills all the inclusion and none of the exclusion criteria. The IRT will assign a randomization number to the patient, which will link the patient to a treatment arm.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for patients will be reviewed and approved by a member of the Randomization Group.

6.4 Treatment masking

The intent of masking is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. Bias could arise from the influence that the

knowledge of a specific treatment assignment may have on the recruitment and allocation of subjects, their subsequent care, the assessment of end points, the handling of withdrawals, and so on. The essential aim of masking, therefore, is to prevent identification of the treatments by the investigator, subject, and others associated with the conduct of the study until all such opportunities for bias have passed.

This study will be double-masked, with patients randomized to be treated with brolucizumab 6 mg or aflibercept 2 mg. All members of the Sponsor team will be masked to treatment assignments while the study is in progress. In addition, the biostatistician who is directly involved in the conduct of the study (i.e. involved in subject level discussions or direct interaction with sites) will remain masked to treatment assignments while the study is in progress. Sponsor personnel who have access to treatment codes will not divulge the codes to subjects, investigators, site staff or Sponsor.

Unmasking of investigators and personnel directly involved in the conduct of the study will only occur in the case of subject emergencies (Section 6.6.2), and then at the time of the final analysis (Section 11), at the conclusion of the study.

In the event of a medical emergency or an adverse event (AE) during the study where the knowledge of subject treatment is required (e.g. in case of Suspected Unexpected Serious Adverse Reactions (SUSAR)), an individual investigator will have the ability to unmask the treatment assignment for a specific subject. The investigator should notify the Sponsor prior to unmasking a subject, if there is sufficient time. Further, the Sponsor must be informed whenever the randomization code is broken and be informed about the reasons for unmasking.

Each site must have both masked and unmasked investigators available. The investigator who performs the injection will be unmasked to the treatments as will any other site personnel who have been delegated responsibility for working with the IP. The unmasked site personnel and unmasked injecting investigator must not perform BCVA, complete ophthalmic examination, disease activity assessments or administer the VFQ-25. Also, the unmasked site personnel and unmasked injecting physician must not perform assessment of any ocular or non-ocular safety parameters, or assess causality AEs for subjects during the course of the study except an event reported immediately following IVT injection.

The unmasked investigator/site personnel should, however, assess subject safety immediately following injection. Once the designated roles are determined, the unmasked investigator/site personnel not be switched at any time after randomization to masked role. Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this masked study.

Treatment masking of individual subjects will remain intact until the final database lock has occurred by ensuring: Randomization data are kept strictly confidential until the time of unmasking and will not be accessible by anyone else involved in the study except the unmasked/treating investigator. During and after database lock at Week 48, the masked personnel and subjects will remain masked to the treatment assignment until the conclusion of the study.

Unmasked monitors will be available to perform study medication accountability and to deal with study issues involving the unmasked investigator or unmasked site staff.

[redacted]

An independent, masked review of fundus photography, fluorescein angiography and optical coherence tomography (OCT) images for subjects enrolled in the study will be performed at a Central Reading Center (CRC).

The randomization codes associated with subjects from whom PK and ADA samples are taken will be disclosed to PK analysts who will keep PK results confidential until database lock.

Unmasking will occur in the case of subject emergencies and at the conclusion of the study.

Table 6-3 Masking levels

	Time or Event		
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single subject unmasked)**
Subjects/Patients	B	B	B
Site staff	B	B	B
Unmasked site staff (see text for details)	B	UI	UI
Global Clinical Supply and Randomization Office	UI	UI	UI
Unmasked sponsor staff (see text for details)	B	UI	UI
Statistician/statistical programmer/data analysts	B	B	B
All other sponsor staff not identified above	B	B	B

B Remains masked
UI Allowed to be unmasked on individual patient level

6.5 Dose escalation and dose modification

Investigational treatment dose adjustments are not permitted.

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

6.5.1 Dose modifications

Treatment dose adjustments and/or interruptions are not permitted unless interruptions are warranted by an AE.

6.6 Additional treatment guidance

6.6.1 Treatment 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 captured by the unmasked investigator staff or by unmasked field monitor on the appropriate study treatment dispensing form.

[redacted]

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.

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject 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 subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject 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.

If the treatment code needs to be broken in the interest of subject safety, the investigator is encouraged to contact an appropriate Sponsor representative prior to unmasking if there is sufficient time.

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

- protocol number
- study drug name (*if available*)
- subject 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.

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

6.7 Preparation and dispensation

Each study site will be supplied with study drug.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label. Unmasked study staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the medication kit 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 patient number.

[redacted]

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 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 unmasked investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the IB. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) 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 subject except for the medication number.

The unmasked investigator designated site personnel 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 unmasked monitors during site visits or remotely and at the completion of the trial. Study site will be asked to return all unused study drug and packaging.

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

6.7.1.2 Handling of additional treatment

6.7.2 Instruction for prescribing and taking study treatment

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

There will be two treatment phases for IVT injections with different timing for brolucizumab and aflibercept treatment arms (loading phase and maintenance phase).

Brolucizumab 6 mg will be administered by IVT injection in accordance with supplied instructions for use. Subjects in the brolucizumab 6 mg arm will receive loading doses at Baseline, Week 4 and Week 8. After the loading doses, subjects will receive q12w treatment unless there is disease activity as assessed by the investigator during one of the scheduled DAA visits. If disease activity is identified, the subject will be assigned to receive injections q8w thereafter, up to Week 44.

Aflibercept 2 mg will be administered by IVT injection in accordance with instructions for use specified in the label. Subjects in the aflibercept 2 mg arm will receive loading doses at Baseline, Week 4 and Week 8. After the loading doses, subjects will receive q8w treatment starting at Week 16 and up to Week 40. DAAs will be conducted by the evaluating/masked investigator for masking purposes and will not influence the treatment interval.

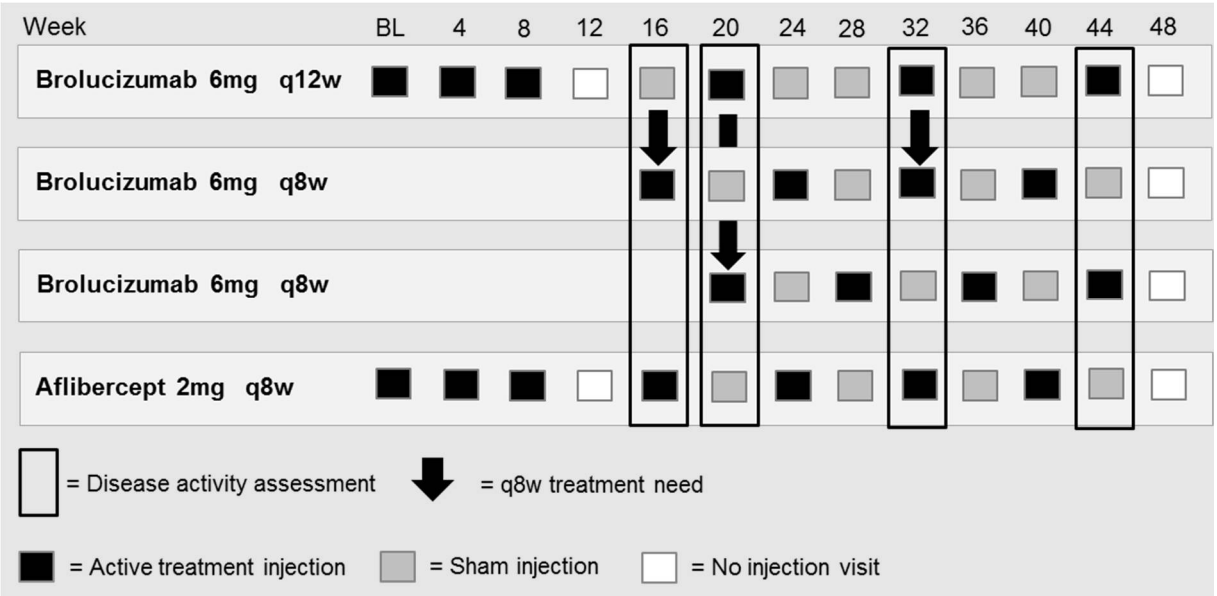
The IVT injection procedure for brolucizumab and aflibercept, including aseptic and antimicrobial requirements, will be performed according to local clinical practice. The sham injection should mimic an IVT injection including the aseptic and antimicrobial

[redacted]

requirements. The tip of the sham injection syringe (the hub without a needle) will be placed on the eye for the approximate amount of time it would take to perform an IVT injection.

In both treatment arms, there will be no treatment injection administration on Week 12 and 48.

Figure 6-1 Dosing schedule



Disease activity assessment (DAA)

The concept of the brolucizumab q12w/q8w regimen is to allocate subjects according to their individual treatment needs to either a q12w or a q8w treatment schedule. The initial schedule is q12w and a subject will remain on q12w as long as the masked investigator does not identify disease activity which in his opinion requires more frequent anti-VEGF treatment.

Disease activity will be assessed by the masked Investigator for all subjects in order to maintain masking. The assessment will only be performed at the prespecified DAA visits at:

- Week 16 and Week 20, during the first q12w treatment interval (i.e. for brolucizumab subjects 8 and 12 weeks after the last loading injection) to make sure that subjects with a high treatment need are identified early on,
- Week 32, following second q12w treatment interval
- Week 44, to document the adequacy of the q12w treatment schedule at the end of treatment (EOT) period (without having impact on the subject's treatment schedule).

The assessment of the disease activity is at the discretion of the masked investigator. He/she should apply their own expert judgement when assessing q8w treatment need. Disease activity criteria outlined below might be considered as guidance.

Disease activity criteria at Week 16:

- Decrease in BCVA of ≥ 5 letters compared with Baseline
- Decrease in BCVA of ≥ 3 letters and CSFT increase ≥ 75µm compared with Week 12
- Decrease in BCVA of ≥ 5 letters due to nAMD disease activity compared with Week 12

[redacted]

- New or worse intraretinal cysts (IRC) / intraretinal fluid (IRF) compared with Week 12

Disease Activity Criterion at Weeks 20, 32 and 44:

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

If DAA reveals a need for q8w treatment the subject will be assigned to receive injections q8w thereafter, up to the end of the study. Only DAA at the scheduled DAA visits have an impact on the subject's treatment schedule (except Week 44).

The outcome of the DAA will be captured in the IRT system. The IRT system will make the necessary changes to the dosing schedule as per the masked investigator's assessment of disease activity.

A subject randomized to brolucizumab 6 mg who misses Week 16 will undergo disease activity assessment at Week 20 as he/she would have done if the visit had not been missed. If, however, subject misses Week 20 or Week 32 visit, then the subject will be assumed to have had a q8w treatment need at this missed visit and will be assigned to a q8w schedule at the next visit (i.e. at the next visit the subject will receive an active injection) up to study exit. The IRT system will make the necessary changes once the missed visit is registered.

Intravitreal injection

The IVT injection will be carried out under controlled, aseptic conditions per local clinical practice and in accordance with supplied instructions for use (brolucizumab 6 mg) or instructions for use specified in the label (aflibercept 2 mg).

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 (IOI); therefore, the investigator must verify that these conditions are not present in study eye prior to every injection.

If any signs of intraocular inflammation is present, then an IVT injection must not be performed. Additional ophthalmic examination and imaging should be performed to evaluate IOI (see Section 8.4.3).

If IOI is confirmed, subjects should be treated for IOI according to clinical practice and closely monitored since they may be at risk of developing retinal vasculitis and/or retinal vascular occlusion. If subject develops retinal vasculitis and/or retinal vascular occlusion based on the investigator's evaluation, the study treatment must be discontinued.

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

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

Sham injection

At all applicable visits from Week 16 to Week 44, inclusive, a sham treatment will be performed to maintain subject masking. For the sham treatment the tip of an injection syringe (the hub without a needle) will be used.

[redacted]

7 Informed consent procedures

Eligible patients may only be included in the study after providing (witnessed, where required by law or regulation), IEC approved informed consent.

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the patient informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification (IN) or an aggregate safety finding. As new information becomes available, informed consent to be updated and then must be discussed with the subject.

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 requirements.

Male patients must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

During the COVID-19 pandemic that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and documented (e.g. the presence of an impartial witness, sign/dating separate informed consent forms (ICFs) by trial participant and person obtaining informed consent, etc.). Remote informed consent should be appropriately documented and confirmed by way of standard informed consent procedures at the earliest opportunity when the subject will be back at the trial sites.

8 Visit schedule and assessments

Assessment schedule lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects 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 recorded on the CRF.

If the COVID-19 pandemic limits or prevents on-site study visits, study treatment could not be administered and other study assessments may not be performed. Alternative methods of safety monitoring may be implemented. Depending on local regulations, site capabilities and patient's visit status in the study, phone calls or virtual contacts (e.g. teleconsult) can be performed for safety follow-up for the duration of the pandemic, until it is safe for the participant to visit the site again.

[redacted]

Table 8-1 Assessment Schedule

Period	**Screening**	**Treatment**																	**End of Treatment/Study**
Visit Name	**Screening / Visit 0**	**Baseline / Visit 1**	**Visit 1b/ 6h post dose**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**EOS**[2]
Days	**-14 to -1**	**1**	**1**	**2**	**8 ±1**	**15 ±1**	**22 ±3**	**29 ±3**	**57 ±3**	**85 ±7**	**113 ±7**	**141 ±7**	**169 ±7**	**197 ±7**	**225 ±7**	**253 ±7**	**281 ±7**	**309 ±7**	**337 ±7**
Weeks	**-2 to -1**	**1**	**1**	**1**	**2**	**3**	**4**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Time (post-dose)	**-**	**-**	**6h ±1**	**24h ±4**	**168h ±24**	**336h ±24**	**504h ±72**	**672h ±72**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Informed consent[3]	X																		
Demography	X																		
Medical history/current medical conditions	X																		
Physical Examination[4]	X																		
Concomitant medications	X	X	X[5]	X[5]	X[5]	X[5]	X[5]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X[5]	X[5]	X[5]	X[5]	X[5]	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion / Exclusion criteria	X	X																	
Visual Function Questionnaire-25		X											X						X
Vital Signs	X[6]	X[6]						X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test (urine)[7]	X	X						X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics Informed Consent	X																		
PK blood collection[5,8]		X	X	X	X	X	X	X[15]											
anti-drug antibody in blood	X							X		X			X			X			X
Hematology[8]	X									X									X

[redacted]

Period	**Screening**	**Treatment**																	**End of Treatment/Study**
Visit Name	**Screening / Visit 0**	**Baseline / Visit 1**	**Visit 1b/ 6h post dose**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**EOS**[2]
Days	**-14 to -1**	**1**	**1**	**2**	**8 ±1**	**15 ±1**	**22 ±3**	**29 ±3**	**57 ±3**	**85 ±7**	**113 ±7**	**141 ±7**	**169 ±7**	**197 ±7**	**225 ±7**	**253 ±7**	**281 ±7**	**309 ±7**	**337 ±7**
Weeks	**-2 to -1**	**1**	**1**	**1**	**2**	**3**	**4**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Time (post-dose)	**-**	**-**	**6h ±1**	**24h ±4**	**168h ±24**	**336h ±24**	**504h ±72**	**672h ±72**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Clinical Chemistry[8]	X									X									X
Urinalysis[8]	X									X									X
Best corrected visual acuity	X[9]	X[9]						X	X	X[9]	X	X	X[9]	X	X	X[9]	X	X	X[9]
Intraocular Pressure (IOP)	X[9]	X						X	X	X	X	X	X	X	X	X	X	X	X[9]
Ophthalmic Exam[10,1]	X[9]	X						X	X	X	X	X	X	X	X	X	X	X	X[9]
Spectral Domain Optical Coherence Tomography[1]	X[9]	X						X	X	X	X	X	X	X	X	X	X	X	X[9]
Fluoroscein angiography[1]	X[9]									X									X[9]
[redacted]																			
Color fundus photo[1]	X[9]									X									X[9]
Disease activity assessment											X	X			X			X	
Contact IRT	X	X[13]						X	X		X	X	X	X	X	X	X	X	
Administration of study drug or sham[14]		X						X	X		X	X	X	X	X	X	X	X	

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[1] Additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation.

[redacted]

Period	Screening	Treatment																	End of Treatment/Study
Visit Name	Screening / Visit 0	Baseline / Visit 1	Visit 1b/ 6h post dose	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	EOS[2]
Days	-14 to -1	1	1	2	8 ±1	15 ±1	22 ±3	29 ±3	57 ±3	85 ±7	113 ±7	141 ±7	169 ±7	197 ±7	225 ±7	253 ±7	281 ±7	309 ±7	337 ±7
Weeks	-2 to -1	1	1	1	2	3	4	4	8	12	16	20	24	28	32	36	40	44	48
Time (post-dose)	-	-	6h ±1	24h ±4	168h ±24	336h ±24	504h ±72	672h ±72	-	-	-	-	-	-	-	-	-	-	-

[2] All exit procedures should be followed, regardless of when the subject exits the study. Visit should be at least 4 weeks from last dose of study treatment. Patient report outcome (PRO) will not be administered on EOS if different from Week 48 visit.
[3] Must be signed/dated prior to performing any study procedures, including screening procedures.
[4] All clinically significant findings will be recorded as medical history or adverse events, as appropriate. Includes height and weight.
[5] If PK Consent was provided (in subset of PK subjects).
[6] In case there is an elevated blood pressure measurement as specified in the exclusion criteria the blood pressure measurement should be repeated after 20 minutes. If the repeat measurement is elevated, then the patient is not eligible to be enrolled into the study.
[7] Required for all female subjects of childbearing potential. Urine pregnancy test will be performed unless local regulations require a serum pregnancy test.
[8] All blood draws and collection of urine should be performed prior to receiving the IVT or sham injection and prior to injection of fluorescein dye.
[9] Both eyes
[10] Includes fundus and slit lamp examination. Pupil dilation for the fundus examination is at the discretion of the Investigator.
[redacted]
[13] Patients will be randomized to brolucizumab 6 mg/50 µL or aflibercept 2 mg/50 µL.
[14] Beginning at Week 16, when subjects do not receive an active injection, they will receive a sham injection. The injection may be performed at a later time, as long as it is within 7 days of the scheduled visit and within the visit window.
[15] No need to additionally collect PK blood at visit 6 for PK consent participants. The blood drawn for anti-drug antibody in blood could also be used for PK analysis at the same visit.

[redacted]

8.1 Screening

Screening

A screening period of up to 2 weeks will be used to assess eligibility. The screening period starts with the signing of the ICF.

One time rescreening of patients will be allowed, except for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the patient. As long as testing can be repeated within 14 days of the first screening, the other screening assessments do not need to be repeated. If rescreening is to occur beyond 14 days from the original screening visit date, then all screening procedures must be repeated.

Medical judgement should be exercised to ensure that treatment is not withheld in order for a patient to participate in the study.

8.1.1 Information to be collected on screening failures

All patients who have signed informed consent but not entered into the next period will have the study completion eCRF pages for the screening period, demographics, inclusion/exclusion, and serious adverse event (eSAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

Patients who are randomized and fail to start treatment, e.g. patients randomized in error, will be considered an early terminator. The reason for early termination will be recorded on the appropriate CRF.

8.2 Subject demographics/other baseline characteristics

The following information will be collected/documented at screening/Baseline visit for each patient:

- Age
- Gender
- Race
- Physical Exam
- Vital signs
- Study eye
- Visual acuity
- Optical Coherence Tomography (OCT)
- Fluoroscein angiography (FA)
- Color Fundus Photo
- [redacted]
- Visual Function Questionnaire (VFQ-25)
- Intraocular pressure (IOP)
- Laboratory test results including urinalysis, ADA and PK
- Concomitant medications
- Past medical history and current medical condition

[redacted]

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy

The following assessments will be performed to evaluate the effect of brolucizumab and aflibercept on visual function, retinal structure and vascular leakage:

- Best-corrected visual acuity with ETDRS-like chart at initial testing distance of 4 meters,
- Optical Coherence Tomography,
- Color Fundus Photography and Fluorescein Angiography.

8.3.1 Visual acuity

Visual acuity will be assessed at every study visit using best correction determined from protocol refraction (BCVA). BCVA measurements will be taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts. The details of the procedure and training materials are provided in the applicable manual. Certification of the assessment procedures and assessors will occur prior to any evaluation of study patients.

8.3.2 Optical coherence tomography

Spectral Domain Optical Coherence Tomography (SD-OCT) will be assessed in the study eye at every study visit and in both eyes at screening and EOS.

These assessments will be performed by certified technician or investigator at the sites and should be performed prior to any study drug administration. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study patients. Masked evaluating investigators will evaluate the SD-OCT to assess the status of disease activity. The SD-OCT machine used for an individual patient should not change for the duration of the study.

The images will be reviewed by a Central Reading Center (CRC) to ensure a standardized evaluation. At screening, SD-OCT images will be submitted to the CRC for determination of eligibility. For further procedural details, the investigator should refer to applicable manual provided by the CRC.

8.3.3 Color fundus photography and fluorescein angiography

Color fundus photography and fluorescein angiography (FA) will be performed in both eyes at screening and EOS and in the study eye only at Week 12.

These assessments will be performed by certified technician or investigator at the sites and should be performed prior to any study drug administration. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study patients.

The images will be reviewed by a CRC to ensure a standardized evaluation. At screening, retinal images will be submitted to the CRC for determination of eligibility. FA images from previous routine evaluations may be used for the screening FA as long as they were performed within 14 days of the screening visit using CRC-certified equipment and examiners. For further procedural details, the investigator should refer to applicable manual provided by the CRC.

[redacted]

Additional images will be taken in case of any signs of intraocular inflammation. Optical coherence tomography, color fundus photography and fluorescein angiography (preferably wide-field or with peripheral sweeps) should be performed for safety evaluation as described in Section 8.4.3.

[redacted]

8.3.5 Appropriateness of efficacy assessments

The selected efficacy assessments are the ones used in the clinical practice to assess the functional and anatomical changes of the affected macular area due to nAMD. BCVA as a measure of retinal function and SD-OCT images to analyze anatomical changes are standard assessments to monitor nAMD and potential treatment effects in routine practice and clinical trials. Likewise established FA is used to assess the type of CNV lesion and determine the vascular leakage; and Color Fundus that helps classifying potential presence of retinal pathology such as fibrosis or geographic atrophy.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed. If the COVID-19 pandemic limits or prevents on-site study visits, phone calls or virtual contacts should be conducted for safety monitoring and discussion of the subject´s health status, until the subject can again visit the site.

For details on AE collection and reporting, refer to AE section.

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. The examination will be performed at screening and at EOT/EOS visit. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the eCRF capturing Medical History. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded on the appropriate AE eCRF page.
Vital signs	Sitting blood pressure and pulse rate will be collected at all visits before treatment. Vital signs include assessment of sitting blood pressure (systolic and diastolic pressure in mm Hg) and pulse (beats per minute). In case there is an elevated blood pressure measurement as specified in the exclusion criteria, at the screening or Baseline visits, the blood pressure measurement should be repeated after 20 minutes. If the repeat measurement is elevated, then the patient is not eligible to be enrolled into the study.

[redacted]

Assessment	Specification
	On days when study drug is administered, vital signs will be measured before administration of study medication. The results will be recorded in the eCRF.
Height and weight	Height and weight will be measured at the screening visit only as part of the physical examination. Height in centimeters (cm) and body weight (to the nearest 0.1 kg, in indoor clothing but without shoes) will be measured at screening only. The results will be recorded in the eCRF.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected at applicable visits. Details on the collections, shipment of the samples and reporting of the results by the central laboratory are provided to investigators in the laboratory manual.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/current medical conditions/AE eCRF page as appropriate.

The following laboratory evaluations will be performed:

- **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.
- **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).
- **Urinalysis:** specific gravity, pH, color, glucose, blood, ketones, bilirubin, and microscopic examination (WBC, RBC, epithelial cells, bacteria, mucus, casts, and crystals).

If the COVID-19 pandemic limits or prevents on-site study visits, the method of collection of samples may be modified by Novartis if applicable and if modified, will be communicated to the Investigator.

8.4.2 Pregnancy and assessments of fertility

High effective contraception is required for women of childbearing potential during the study and for 3 months after stopping the investigational medication.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy,
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female patient, regardless of reported reproductive/menopausal status at screening/Baseline.

[redacted]

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 at screening visit and then at EOT/EOS visit. During study, monthly urine pregnancy testing will be performed and results captured in the source documents.

8.4.3 Ophthalmic examination

The ophthalmic exam will be performed in the study eye at every study visit and in both eyes at screening and EOT/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 study eye.

The ophthalmic exam will consist of the following:

Anterior biomicroscopy (slit lamp examination) will be completed at every visit (scheduled and unscheduled) to examine the anterior segment structures (e.g., eyelids/lashes, conjunctiva, cornea, anterior chamber, iris, lens and anterior part of the vitreous) of the study eye (Additional examination of the fellow eye will be done at the discretion of the investigator). The outcome of the examination will be recorded in the source documents.

Slit lamp examination must be carefully performed before study treatment for signs of IOI. If there is any signs of IOI, severity of anterior chamber cells and flare should be assessed according to the standardization uveitis nomenclature (SUN) working group grading system.(Jabs et al., 2005). The test results will be recorded in the source documents (e.g., ophthalmic examination tool) and captured in the appropriate eCRF as applicable.

Measurement of **Intraocular pressure measurement (IOP)** will be conducted according to the routine clinical practice (using an applanation tonometer, non-contact 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 in the study eye, pre-dose and post-dose at every scheduled visit. The values recorded in mmHg will be entered into the eCRF.

Treatment and close monitoring of IOP should be performed by the investigator for any non-transient elevation in intraocular pressure (≥25 mmHg). Intravitreal procedure is not recommended unless normalization of the IOP has been achieved. Post dose IOP should be assessed after every IVT injection, within 60 minutes after injection and if ≥25 mmHg, assessment should be repeated until back to normal.

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 eCRF.

Posterior segment (indirect fundus) examination will be conducted by the investigator at the screening visit for both eyes. An examination of the peripheral retina must also be conducted to ensure that the intravitreal injection can be safely performed. Posterior segment examination must be performed carefully before each study treatment. The results of the examination

[redacted]

including any abnormalities (e.g. vitreous cells/haze, retinal tear/detachment, hemorrhage and vascular occlusion, vasculitis, etc.) should be recorded in the source documents. If there are any signs of IOI, vitreous cells and haze should be assessed using National Institutes of Health (NIH) grading system (Nussenblatt et al., 1985). The outcome of the examination will be documented in the source document (e.g. ophthalmic examination tool) and appropriate eCRF page as applicable.

Instruct the patient to contact the site for any changes in vision or any symptoms of inflammation between scheduled visits. Every effort should be made to bring the subject for immediate examination. When IOI, retinal vasculitis, and/or retinal artery occlusion (RAO) is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and conduct optical coherence tomography, fluorescein angiography and color fundus photography (preferably wide-field or with peripheral sweeps). These additional assessments will be documented in the source and appropriate eCRF pages as applicable. The images are requested to be uploaded onto the CRC portal. If subject develops retinal vasculitis and/or retinal vascular occlusion based on the investigator's evaluation, the study treatment must be discontinued. In addition, as some of the subjects who experience IOI may be at risk of developing retinal vasculitis and/or retinal vascular occlusion, the subject should be closely monitored and managed according to clinical practice.

8.4.4 Other safety evaluations

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population. If there are any signs of IOI, additional assessment will be performed as described in Section 8.4.3.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

8.5.1.1 Patient Reported Outcomes (PRO)

The impact of brolucizumab on subject visual function will also be assessed by a visual function questionnaire using the National Eye Institute VFQ-25 which is a validated instrument that has been used in many studies of patients with nAMD. The VFQ-25 was developed to address the need to measure a patient's subjective assessment of vision-related QoL (Mangione et al 2001). This is part of the 51-item NEI-VFQ which was developed based on feedback from patients to measure vision-targeted functioning and the impact of vision problems on Health Related Quality of Life (HRQL) across a number of common eye conditions. This allowed the developers to identify the content areas and aspects of visual disability that were most important and relevant to AMD patients.

At Baseline and Weeks 24 and EOS the VFQ-25 will be completed and captured by masked site staff on behalf of the subjects, at sites where local language versions are available, validated, and approved by the IEC/IRB. All these questionnaires should be completed before subjects see the study physician where applicable.

[redacted]

A detailed training manual relating to the administrative procedures of the questionnaires will be provided to the sites.

Completed questionnaires will be reviewed and examined by the masked/evaluating investigator, before the clinical examination, for responses that may indicate potential AE or SAE. If AEs or SAEs are confirmed, then the physician must record the events as per instructions given in Section 10.1.1 and Section 10.1.2.

8.5.2 Pharmacokinetics

Systemic brolucizumab exposure will be assessed in approximately 24 consented subjects (approximately 12 subjects per treatment arm to maintain masking). Serum samples will be taken (according to manual provided by lab) at Day 1 prior to the first injection and at the following time points after the first injection: 6h post-injection on Day 1, Day 2, Day 8, Day 15, Day 22, and Day 29 prior to the second injection.

Further details on sample collection, numbering, processing and shipment can be found in the central lab manual.

8.5.3 Other Assessments

Anti-drug antibodies (immunogenicity)

Collection of blood for ADA assessment will be done at screening, Weeks 4, 12, 24, 36, 48 and exit/premature discontinuation in brolucizumab treatment arm (collection of ADA sample will be done in both treatment arms to maintain masking). Systemic exposure of brolucizumab will be measured concomitantly with ADA levels for interpretation purposes, no pharmacokinetic parameters will be determined from brolucizumab exposure measured at the above-mentioned timepoints (except, at visit 6 the blood drawn for anti-drug antibody in blood would also be used for PK analysis at the same visit, for the PK consent participants.). Additional pharmacodynamic assessment may be conducted on the samples wherever permitted by local regulation. Blood draws should take place prior to the injection/sham. A standardized procedure for the collection, processing, storage and shipment of these blood samples is provided by the central laboratory. Further details on sample collection, numbering, processing and shipment can be found in the central lab manual.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

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

The investigator should discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision

- Pregnancy
- Use of prohibited treatment as per recommendations in Table 6-2
- Any situation in which study participation might result in a safety risk to the subject
- Subject develops a retinal vasculitis and/or a retinal vascular occlusion event
- Unsatisfactory therapeutic effect
- Patient's condition no longer requiring study treatment

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section,). The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the appropriate eCRF page. **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Section 6.6.2.

9.1.2 Withdrawal of informed consent /Opposition to use data/biological samples

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent/opposition to use data/biological samples occurs only when a subject:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use subject's data and biological samples)

and

No longer wishes to receive study treatment and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

[redacted]

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

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 subject 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 subject's study withdrawal should be made as detailed in the assessment table.

Discontinued subjects will not be replaced.

Novartis will continue to keep and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.1.3 Lost 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 subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

[redacted]

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit (e.g. LPLV), and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision (e.g. Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 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 patient or clinical investigation patient after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

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

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

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity 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
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its relationship to the study procedure
4. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.

[redacted]

5. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
6. action taken regarding study treatment.

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

- Dose not changed
- Drug interrupted/withdrawn

7. its outcome
    a. not recovered/not resolved;
    b. recovered/resolved;
    c. recovering/resolving,
    d. recovered/resolved with sequelae;
    e. fatal; or unknown.

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator Brochure (IB)

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 subjects with the underlying disease.

10.1.2 Serious adverse events

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:

- fatal
- life-threatening

[redacted]

Life-threatening in the context of a SAE refers to a reaction in which the subject 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 the ICH-E2D Guidelines).

- 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
  - 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
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - 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
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

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 subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". 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.

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

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

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after last study visit must be reported to Novartis/safety within 24-hours of learning of its occurrence.

1. SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis/

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.

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 CMO&PS Department associate may urgently require further information from the investigator for health authority

[redacted]

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 (EC) in accordance with EU Guidance 2011/C172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy.

To ensure subject 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 pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject 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 recorded in the dose administration record (DAR) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

The RTH258 program level Data Monitoring Committee (DMC) will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will assess at defined intervals the progress of a clinical trial, safety data, and critical efficacy variables and recommend to the sponsor whether to continue, modify or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

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

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

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

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

[redacted]

11.2 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 are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment (s) dispensed to the subject 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) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unmasked and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis (or delegated CRO) representative will review the protocol and data capture requirements (i.e. 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 subject 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 (or delegated CRO) 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 subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, retinal imaging, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

[redacted]

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 subjects will be disclosed.

12 Data analysis and statistical methods

The primary efficacy and safety analysis will be based on data up to and including Week 48. This will be performed once all subjects complete the EOS visit or discontinue from the study. Summary statistics will be presented by treatment group unless otherwise specified. For continuous variables, summary statistics will generally include: n, mean, standard deviation, median, quartiles, minimum, and maximum. For categorical variables, these will generally include: n, frequency and percentage in each category. [redacted]

Further technical details and discussions of the statistical considerations will be provided in the SAP.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The **Randomized Analysis Set** (RAS) consists of all randomized patients. Patients are considered randomized when they had been deemed eligible for randomization by the investigator and given a randomization number. Subjects will be analyzed according to the treatment assigned to at randomization.

The **Full Analysis Set** (FAS) comprises all subjects to whom study treatment has been assigned by randomization and who receive at least one IVT injection of the study treatment. The full analysis set will serve as the primary analysis set for all efficacy analyses. According to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The **Safety Set** includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment arm from which they received majority of treatments up to and including Week 44.

Supportive analyses of the primary and key secondary efficacy endpoints will include analysis using the **Per-Protocol Set** (PPS). PPS is a subset of the Full Analysis Set and will exclude subjects with protocol deviations (PDs) and analysis restrictions (ARs) that are expected to majorly affect the validity of the assessment of efficacy at Week 48 including for e.g. lack of compliance (including missed treatments and treatment misallocation), missing data, prohibited concomitant medication and deviation from inclusion/exclusion criteria. Confounded data or

[redacted]

discontinuation from treatment due to lack of efficacy and/or safety do not constitute a reason for exclusion from the PPS.

Before the database lock, the relevant protocol deviations will be identified at the subject level in the database. After the database lock, analysis restrictions will be derived in the analysis database. Censoring applied in relation to the specific PDs / ARs will be specified as well.

The FAS will be the analysis set for the primary estimand as defined in Table 12-1. However, when assessing the robustness of the overall efficacy conclusions, considerations will be given to the analysis based on the primary estimand using FAS and the supplementary estimand (see Table 12-1) using PPS, i.e., similar conclusions on non-inferiority based on both estimands are expected. Inconsistencies in key efficacy study results between the FAS and PPS will be examined and discussed in the clinical study report (CSR).

The Pharmacokinetic analysis set includes all subjects who provide an evaluable PK profile for brolucizumab. A profile is considered evaluable if all of the following conditions are satisfied:

- Subject receives the planned first dose of brolucizumab
- Subject provides at least one primary PK parameter of brolucizumab (Cmax and AUC)

12.2 Subject demographics and other baseline characteristics

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

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

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

12.3 Treatments

The Safety set will be used for the analyses below.

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

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

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

[redacted]

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The primary endpoint is the change from Baseline in BCVA at Week 48. The first key secondary endpoint is average change in BCVA from Baseline over the period Week 36 through Week 48. For each subject, this endpoint is defined as the average of the changes from Baseline to Week 36, 40, 44 and 48. The primary analysis of the primary and first key secondary endpoints will be based on the FAS.

12.4.2 Statistical model, hypothesis, and method of analysis

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

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

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

48 = Week 48, 36-48 = Week 36 through 48, R= brolucizumab 6 mg, A= aflibercept 2 mg

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

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

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

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

For the test of non-inferiority, a two-sided 90% CI for the treatment difference will be derived from an analysis of variance (ANOVA) model with treatment, Baseline BCVA categories (≤ 55, $\geq$56-$\leq$70, ≥ 71 letters) and age categories (< 75, ≥ 75 years) as factors. In order to demonstrate non-inferiority, the lower limit of the two-sided 90% CI for the treatment difference (brolucizumab 6 mg – aflibercept 2 mg) must be greater than -4 letters representing the noninferiority margin.

The primary estimand and supplementary estimand of interest are described in Table 12-1 below, together with their key attributes, and will be discussed in further detail in the SAP.

[redacted]

Table 12-1 Primary and supplementary estimands

Estimand	Estimand definition	Analysis set	Statistical methods (Including strategy for imputation/replacement of missing/censored data)
Primary estimand	Difference in change from baseline in BCVA at Week 48 excluding the effect of switching to alternative nAMD medication in the study eye	FAS	Analysis of variance (ANOVA) model including terms for treatment, baseline BCVA (≤55, ≥56-≤70, ≥ 71 letters) and age category (<75, ≥75 years), and using LOCF imputation/replacement for missing/censored data.
Supplementary estimand	Difference in change from baseline in BCVA at Week 48 for patients adhering to the protocol as per the PPS definition	PPS	ANOVA model as per the primary estimand. LOCF imputation/replacement for missing/censored data

12.4.3 Handling of missing values/censoring/discontinuations

Missing BCVA values will be imputed by LOCF (Last Observation Carried Forward) as a primary approach. For subjects with no post-Baseline BCVA value, the Baseline value will be carried forward. Data collected after start of alternative nAMD treatment in the study eye (e.g. other anti-VEGF treatment, as further detailed in the SAP) will be censored for the primary analysis. All non-missing post-Baseline values including assessments done at unscheduled visits will be used when implementing the LOCF imputation. From an estimand perspective, the main focus is to adequately reflect in the analysis unfavorable study outcome related to the treatment (e.g. lack of efficacy, safety problems).

The LOCF approach is expected to be sensitive to an early study termination due to lack of efficacy assuming that such lack of efficacy is reflected in the last observed BCVA measurement. In case of the use of alternative treatment for the underlying disease, data collected after the start of such a treatment would be censored. LOCF will then be based on the last value prior to the start of this treatment, again expecting that this value would reflect the negative BCVA outcome under study treatment. In case of missing data due to lack of safety/tolerability with impairment of the function of the study eye the LOCF method would also provide a sensitive approach to capture such an unfavorable outcome.

In case of missing data occurring independently of the response to study treatment, the LOCF approach assumes stability which seems to be adequate based on historical data both for the maintenance treatment phase (i.e. stabilization of BCVA) and also in case of the absence of any treatment effect. In case of an early study termination during the loading phase, the LOCF method will result in a conservative estimate potentially underestimating the true outcome.

LOCF is an established method within the assessment of efficacy of anti-VEGF treatments in terms of BCVA outcome. It is important to note that non-inferiority studies should follow the main design features (primary variables, the dose of the active comparator, eligibility criteria,

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etc.) as the previously conducted superiority trials in which the active comparator demonstrated clinically relevant efficacy.

Other methods of handling missing or confounded data within sensitivity analyses will be performed, as detailed in the SAP.

12.4.4 Sensitivity and Supportive analyses

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

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

The following subgroups will be analyzed for the primary and first key secondary efficacy endpoints using the primary analysis approach:

- Age category (< 75 years and ≥75 years)
- Gender (male and female)
- Baseline BCVA categories (≤ 55, ≥56-≤70, ≥ 71 letters)
- Baseline CSFT category (< 400, ≥ 400)
- Baseline lesion type (predominantly classic, minimally classic, pure occult)

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Secondary endpoints will be analyzed based on FAS.

Key secondary efficacy endpoints related to dosing regimen:

- q12w treatment status at Week 48 for subjects randomized to brolucizumab 6 mg
- q12w treatment status at Week 48 within the subjects randomized to brolucizumab 6 mg and with no q8w need during the first q12w cycle (Week 16 and Week 20)

The key secondary endpoints will be analyzed based on the FAS with a negative q12 treatment status at Week 48 in case of incomplete active treatment up to Week 48.

The q12w treatment status at Week 48 in brolucizumab 6 mg treatment arm will be presented descriptively together with exact 90% confidence intervals for the proportion of subjects with a positive status: For the (overall) proportion of subjects with a positive q12w treatment status at Week 48, the denominator is all FAS subjects in the brolucizumab 6 mg group, and the numerator is the corresponding number of subjects with no identified q8w-need at Week 16, 20, 32 and 44 (while missing the Week 16 assessment is considered as no q8w treatment needed). For the predictability of the adequacy of q12w treatment based on the absence of disease activity during the first q12w cycle, the denominator is all FAS subjects in the brolucizumab 6 mg group with no identified q8w-need at Week 16 and Week 20 (while missing the Week 16 assessment is considered a no-q8w treatment needed), and the numerator is the corresponding number of

[redacted]

subjects with a positive q12w treatment status at Week 48 (i.e. with no identified q8w-need at Week 16, 20, 32 and 44).

Secondary efficacy endpoints based on BCVA:

- Change in BCVA from Baseline to each post-Baseline visit
- Average change in BCVA from Baseline over the period Week 4 to Week 48
- Average change in BCVA from Baseline over the period Week 12 to Week 48
- Gain in BCVA of 15/10/5 letters or more from Baseline to each post-Baseline visit

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

- Absolute BCVA of 73 letters or more at each visit
- Loss in BCVA of 15/10/5 letters or more from Baseline to each post-Baseline visit

Secondary efficacy endpoints related to anatomy or disease activity:

- Change in CSFTtot from Baseline to each post-Baseline visit
- Average change in CSFTtot from Baseline over the period Week 36 through Week 48
- Average change in CSFTtot from Baseline over the period Week 4 to Week 48
- Change in CSFTns from Baseline to each post-Baseline visit
- Change in area of CNV within the lesion from Baseline to Weeks 12 and 48
- Presence of subretinal and/or intraretinal fluid (central subfield) at each post-Baseline visit (and specifically Week 16 and Week 48)
- Number of visits with simultaneous absence of subretinal and intraretinal fluid (central subfield) during Week 36 to Week 48
- Presence of subretinal fluid (central subfield) at each post-Baseline visit
- Presence of intraretinal fluid (central subfield) at each post-Baseline visit
- Presence of sub RPE fluid (central subfield) at each post-Baseline visit

Secondary efficacy endpoints related to efficacy at the end of the matched treatment phase:

- Change in CSFTtot from Baseline at Week 16
- Presence of subretinal and/or intraretinal fluid (central subfield) at Week 16
- q8w treatment need identified at Week 16

12.5.2 Safety endpoints

There are no formal safety hypotheses in this study. All safety analyses will be performed using the Safety Set.

Adverse events

Only treatment-emergent adverse events will be presented in the summary tables.

Adverse events will be coded using the MedDRA dictionary and presented by system organ class (SOC) and preferred term (PT). Treatment-emergent AEs will be analyzed based on the number and percentage of subjects with at least one AE in the category of interest. Separate presentations will be provided related to ocular events in the study eye and fellow eye and systemic events. Additional summaries will be provided by severity and causality (separately

[redacted]

assessed for the injection procedure and the drug). Serious adverse events and adverse events leading to discontinuation of study treatment will also be summarized separately.

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

An adverse event of special interest (ESI) is one of scientific and medical interest to the Sponsor and include, but is not limited to, the following:

- Endophthalmitis
- Uveitis: all cases of anterior, posterior, or panuveitis
- ≥30 letter decrease in BCVA compared with Baseline visual acuity
- New retinal tear or detachment
- New diagnosis of geographic atrophy

The number (and proportion) of subjects with adverse events related to identified and potential risks, including AEs of special interest will be summarized by treatment

Ophthalmic examinations

Pre-injection IOP measurements will be presented descriptively (absolute values and change from Baseline). Post-injection IOP measurements will be listed. Presence of fibrosis from color fundus photography by assessment visit will be summarized.

Laboratory tests, vital signs, and special tests

Laboratory data and vital signs will be summarized by presenting shift tables using extended normal ranges (as provided by the central laboratory) with thresholds representing clinical relevant abnormality and by presenting descriptive statistics of raw data and change from Baseline. Values outside the extended normal range will be listed by subject and treatment arm and flagged in data listings.

12.5.3 Pharmacokinetics

Pharmacokinetic parameters will be determined using Phoenix WinNonlin (Version 6.4 or later-Certara L.P) using non-compartmental method(s) for the subjects who had full PK sampling (7 blood sampling points after first dose). PK parameters will be listed by treatment and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. For calculation of PK parameter, Concentrations below LLOQ will be treated as missing.

Serum concentrations will be summarized by treatment and time point for the subjects who had full PK sampling following first dose. Summary statistics will include n (number of values to be reported), arithmetic and geometric mean, median, SD, CV, and geometric CV, minimum and maximum. For the purpose of calculating descriptive statistics for serum concentrations, post-injection concentrations below the LLOQ will be treated half of LLOQ in summary statistics. If the mean was less than the LLOQ, it was reported as being BLQ within the summary tables.

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Table 12-2 Non-compartmental pharamcokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCinf	The AUC from time zero to infinity (mass x time x volume-1)
AUC0-t	The AUC calculated from time zero to the defined time point t (eg.648h)(massx time x volume^{-1})
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (lz) of a semi logarithmic concentration-time curve (time).

12.5.4 DNA

Not applicable

12.5.5 Biomarkers

Not applicable

12.5.6 PK/PD relationships

Not applicable.

12.5.7 Patient reported outcomes

The VFQ-25 questionnaires will be scored (total and subscale scores) at Baseline and Weeks 24 and 48. Absolute scores and the absolute changes from Baseline will be calculated and summarized descriptively.

Further details on the scoring algorithm and analysis will be provided in the SAP.

12.5.8 Anti-drug antibody

Collection of blood for ADA assessment will be done at screening, weeks 4, 12, 24, 36 and 48 prior to the injection/sham, and exit/premature discontinuation. Number and percent of subjects according to their ADA status (negative, positive without boost, treatment-induced, treatment-boosted) will be presented for brolucizumab arm. Patient listings of all ADA titer values will be presented for subjects in brolucizumab arm.

12.7 Interim analyses

Not Applicable.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

In the spirit of bridging concept under ICH E5, a sample size of 175 subjects per treatment arm is sufficient to demonstrate noninferiority (margin = 4 letters) of brolucizumab 6 mg versus aflibercept 2 mg with respect to the BCVA change from Baseline to Week 48 at a one-sided alpha level of 0.05 with a power of approximately 80% assuming equal efficacy and a common standard deviation of 15 letters. A power of at least 80% can be expected for the first key secondary endpoint assuming that averaging BCVA change from Baseline over the 4 time points will not lead to an increase in the standard deviation. To account for a drop-out rate of 10%, a total of 195 subjects will be randomized per treatment arm.

13 Ethical considerations and administrative procedures

13.1 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 with the ethical principles laid down in the Declaration of Helsinki.

13.2 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, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to 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.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, 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.

14 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 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 prohibition, 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.

[redacted]

14.1 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 required for subject safety 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 subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

15 References

References are available upon request

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16 Appendices

Not Applicable.

[redacted]