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Novartis Research and Development

RTH258/Brolucizumab

Clinical Trial Protocol CRTH258AUS04 / NCT03710564

A multicenter, randomized, double-masked Phase 3a study to assess safety and efficacy of brolucizumab 6 mg q4 weeks compared to aflibercept 2 mg q4 weeks in patients with neovascular age-related macular degeneration (nAMD) with persistent retinal fluid (MERLIN)

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List of abbreviations

ACR	Albumin-Creatinine Ratio
[redacted]	[redacted]
AE	Adverse Event
A/G	Albumin/Globulin (ratio)
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMD	Age-related Macular Degeneration
ANOVA	Analysis of Variance
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical (classification system)
BCVA	Best-Corrected Visual Acuity
BL	Baseline
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CFP	Color Fundus Photography
CI	Confidence Interval
cm	Centimeter(s)
CMO&PS	Chief Medical Office and Patient Safety
CNV	Choroidal Neovascularization
CO	Country Organization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease 2019
CRC	Central Reading Center
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSM	Clinical Site Management
CST	Central Subfield Thickness
CTM	Clinical Trial Management
DMC	Data Monitoring Committee
DME	Diabetic Macular Edema
EDC	Electronic Data Capture
EMA	European Medicines Agency
EoS	End of Study
ESI	Event(s) of Special Interest
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	Fluorescein Angiography
FAF	Fundus Autofluorescence
FAS	Full Analysis Set
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
h	Hour
HA	Health Authority

HCG	Human Chorionic Gonadotropin
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IN	Investigator Notification
INR	International Normalized Ratio
IOI	Intra-ocular Inflammation
IOP	Intra-ocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IRE	Intra-retinal Edema
IRF	Intra-retinal Fluid
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
IVT	Intravitreal
kDa	kiloDalton
kg	kilogram(s)
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
mm	Millimeter(s)
mmHg	Millimeter(s) Mercury
nAMD	Neovascular Age-Related Macular Degeneration
No.	Number
OCT	Optical Coherence Tomography
[redacted]	[redacted]
PCR	Protein-Creatinine Ratio
PD	Protocol Deviation
[redacted]	[redacted]
PFS	Prefilled syringe
pH	Potential Hydrogen
prn	As needed (from Latin pro re nata)
PPS	Per-Protocol Set
q	Every (from Latin quaque)
QMS	Quality Management System
RAO	Retinal Arterial Occlusion
RAP	Retinal Angiomatous Proliferation
RAS	Randomized Analysis Set
RBC	Red Blood Cell(s)
RPE	Retinal Pigment Epithelium

[redacted]

RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
scFv	Single-chain Variable Fragment
sCr	Serum Creatinine
SD-OCT	Spectral Domain Optical Coherence Tomography
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
SOM	Site Operations Manual
SOP	Standard Operating Procedure
SRF	Sub-retinal Fluid
SUSAR	Suspected Unexpected Serious Adverse Reaction
TFQ	Trial Feedback Questionnaire
TBL	Total Bilirubin
ULN	Upper Limit of Normal
US	United States
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
w	Week
WBC	White Blood Cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
YAG	Yttrium Aluminum Garnet

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of electronic Case Report Forms (CRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
Investigational drug/ treatment	The drug whose properties are being tested in the study
Masked/evaluating investigator	For the entire study duration and all study subjects, the masked/evaluating investigator is responsible for all aspects of the study (the conduct/supervision of all assessments and treatment decisions except the injection procedures and the safety assessment following the intravitreal [IVT] injections)
Medication number	A unique identifier on the label of medication kits
Mis-randomized subjects	Mis-randomized subjects are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly diagnosed disease.
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes 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/or 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
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study

[redacted]

Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts
Unmasked/treating investigator	For the entire study duration and all study subjects, the treating investigator only performs the IVT injection and assesses patient safety following the IVT injections
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Visual acuity examiner	For the entire study duration and all study subjects, the visual acuity examiner (which could be the masked/evaluating investigator) performs the BCVA assessment and is masked to the assigned treatment
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

[redacted]

Amendment 03

Amendment rationale

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

Changes to the protocol

Major changes are made to the protocol in the following sections:

- Section 1.1 Background, This section was updated to add describe new safety signal from post-marketing case reports.
- Section 6.1.1 Investigational and control drugs, this section was updated to remove the verbiage regarding the allowance of sites to procure their own aflibercept for patients who continue beyond Week 52 as it is no longer applicable. The section was updated to add verbiage around Pre-filled syringe (PFS) use as brolucizumab and/or aflibercept may be provided as PFS.
- Section 6.2.2 Prohibited medication, this section was updated to provide clarity around temporary use of certain medications for Coronavirus disease 2019 (COVID-19).
- Section 6.4 Instruction for prescribing and taking study treatment, this section was updated to provide additional clarification on the masked and unmasked roles.
- Section 6.7.2 Instruction for prescribing and taking study treatment, this section was updated to indicate that intravitreal injection must not be performed in eyes with Intra-ocular Inflammation (IOI) and additional assessments (ophthalmic exam, imaging) are required.
- Section 7 Informed consent procedures, this section was updated to include verbiage regarding providing informed consent updates to subjects as new information becomes available, and remote informed consent during Coronavirus disease 2019 (COVID-19)
- Section 8 Visit schedule and assessments, this section was updated to provide guidance on alternative methods of providing safety monitoring may be implemented if the COVID-19 pandemic limits or prevents on-site study visits.
- Table 8-1, [redacted] This section was also updated to include the Color Fundus Photography acronym (CFP). We also added a footnote indicating that additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation (such as Wide Field FA) and changed that Fundus Autofluorescence (FAF) changed typo from xi to xe.

[redacted]

- Section 8.3.2 Spectral Domain Optical Coherence Tomography New verbiage was added to provide guidance on additional imaging assessment in case of any signs of intraocular inflammation.
- Section 8.3.4 Color fundus photography, this section was updated to fix the inconsistency between the visit assessment schedule and this section.
- Section 8.3.5 Fluorescein Angiography, this section was updated to fix the inconsistency between the visit assessment schedule and this section.
- Section 8.4 Safety/Tolerability, Updated Global template language to provide additional guidance on safety monitoring if the COVID-19 pandemic limits or prevents on-site study visits. In addition, additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation (such as Wide Field FA
- Table 8-2 Assessments & specifications, This section was updated to add additional verbiage to provide guidance to instruct patients when to contact site and what site should do for any signs of or suspected intraocular inflammation, retinal vasculitis, and/or retinal arterial occlusion (RAO). In addition, updated verbiage was added to provide flexibility in timing of post-inject IOP measurement and was updated to indicate that Events of Special Interest (ESI) are subject to change during the study and updated verbiage to be further aligned with the Global RTH program ESIs. This section was updated to fix the inconsistency between the visit assessment schedule and this section.
- Section 8.4.1 Laboratory evaluations, to provide guidance on laboratory evaluation during COVID-19 pandemic.
- Section 8.4.3 Appropriateness of safety measurements, this area provided additional clarification regarding IOI cases and additional assessment that will need to be performed.
- [redacted]
- Section 10.1.3 SAE Reporting, this section was updated to clarify the SAE reporting period
- Section 11.4 Data Monitoring Committee, verbiage to introduce program level Data Monitoring Committee (DMC) in the study protocol where there was no established DMC. This is not applicable for the study protocol with original DMC.
- Section 12 Data analysis and statistical methods, added additional verbiage around COVID-19.
- Section 12.4.2 Statistical model, hypothesis, and method of analysis, verbiage was added to clarify to update the BCVA categories to 2 levels.
- Section 15 References this section has been updated to add references for the new grading systems

[redacted]

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 Authorityapproval 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.

Site Operations Manual (SOM)/Operational Manual

A Site Operations Manual (SOM)/Operational Manual accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

[redacted]

Protocol summary

Protocol number	CRTH258AUS04
Full title	A multicenter, randomized, double-masked Phase 3a study to assess safety and efficacy of brolucizumab 6 mg q4 weeks compared to aflibercept 2 mg q4 weeks in patients with neovascular age-related macular degeneration (nAMD) with persistent retinal fluid (MERLIN)
Brief title	Study of safety and efficacy of brolucizumab 6 mg dosed every 4 weeks compared to aflibercept 2 mg dosed every 4 weeks in patients with retinal fluid despite frequent anti-VEGF injections
Sponsor and Clinical Phase	Novartis; Phase 3a
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to compare safety and efficacy of brolucizumab 6 mg dosed every 4 weeks to aflibercept 2 mg dosed every 4 weeks in those nAMD patients with retinal fluid despite frequent anti-VEGF injections
Primary Objective	The primary objective of this study is to evaluate whether brolucizumab 6 mg dosed every 4 weeks is non-inferior to aflibercept 2 mg dosed every 4 weeks in BCVA change from Baseline to Week 52
Secondary Objectives	1. To assess efficacy of brolucizumab 6 mg dosed every 4 weeks compared with aflibercept 2 mg dosed every 4 weeks with respect to visual acuity (VA) stabilization or improvement at Week52 and 104 2. To evaluate anatomic parameters of disease activity and retinal fluid status in patients treated with brolucizumab 6 mg dosed every 4 weeks compared with aflibercept 2 mg dosed every 4 weeks at Weeks 52 and 104 3. To assess safety and tolerability of brolucizumab 6 mg dosed every 4 weeks compared with aflibercept 2 mg dosed every 4 weeks
Study design	This is a multi-center, double-masked, parallel group study with 2 arms randomized in a 2:1 (brolucizumab:aflibercept) ratio. Total study duration is 104 weeks from Baseline. All participants will have study visits every 4 weeks through Week 104. The primary analysis will be performed at Week 52.
Population	The study population will consist of male and female patients, 50 years or older, who have received recent, frequent anti-VEGF treatments for their nAMD. Approximately 860 patients will be screened to randomize 513 patients in approximately 66 centers in the United States. All patients that are currently enrolled in the study can continue up to 104 weeks if they consent to extend their treatment.
Key Inclusion criteria	• Signed informed consent must be obtained prior to participation in the study • Active CNV lesions secondary to AMD that affect the central subfield (including retinal angiomatous proliferation [RAP] lesions with a CNV component) and which has associated Intra-retinal Fluid (IRF) or Sub-retinal Fluid (SRF) within the central 3 mm subfield in the study eye, confirmed by the Central Reading Center (CRC) at Screening

[redacted]

	• Total area of CNV (including both classic and occult components) must comprise >50 % of the total lesion area in the study eye, confirmed by CRC at Screening • Received first anti-VEGF injection for nAMD in the study eye a minimum of 9 months prior to Screening • If first anti-VEGF injection for nAMD in the study eye received ≤36 months prior to Screening: BCVA ≥55 letters (approximate Snellen equivalent 20/80), inclusive, in the study eye at Screening and Baseline using Early Treatment Diabetic Retinopathy Study (ETDRS) testing; If first anti-VEGF injection for nAMD in the study eye received >36 months prior to Screening: BCVA ≥65 letters (approximate Snellen equivalent 20/50), in the study eye at Screeningand Baseline using ETDRS testing • Received at least 7 anti-VEGF injections in immediate prior 9 months; with the last two injections having been licensed anti-VEGF(aflibercept or ranibizumab) • Demonstrated nAMD fluid improvement or partial response with anti-VEGF therapy as determined by Investigator • Patients must have persistent IRF and/or SRF at Screening and Baseline as determined by Investigator
Key Exclusion criteria	• Any active intra-ocular or peri-ocular infection or active intra-ocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis) in either eye at Screening and Baseline • Total area of fibrosis ≥ 50 % of the total lesion in the study eye, confirmed by CRC at Screening • Fovea of the study eye must not be affected by sub-retinal fibrosis or geographic atrophy by clinical exam and OCT, confirmed by CRC at Screening • Sub-retinal blood affecting the foveal center point and/or ≥ 50 % of the lesion of the study eye, confirmed by CRC at Screening • History or evidence of the following in the study eye: o Intra-ocular or refractive surgery within the 90 day period prior to Screening o Previous penetrating keratoplasty, vitrectomy or ocular radiation o Previous panretinal photocoagulation o Previous treatment with verteporfin photodynamic therapy o Previous submacular surgery, other surgical intervention or laser treatment for AMD o Uncontrolled glaucoma defined as intra-ocular pressure (IOP) >25 mmHg on medication or according to Investigator's judgment at Screening or Baseline

[redacted]

	○ Aphakia and/or absence of the posterior capsule at Screening or Baseline. Yttrium Aluminum Garnet (YAG) laser posterior capsulotomy secondary to uncomplicated cataract extraction with posterior intraocular lens implantation is allowed when >30 days from screening. ○ Intra- or peri-ocular use of corticosteroids during the 6 month period prior to Baseline ○ Use of topical ocular corticosteroids for 30 or more consecutive days within the 90 days prior to Screening • Participation in an investigational drug, biologic, or device study within 30 days or the duration of 5 half-lives of the IP (whichever is longer) prior to first dose Note: observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary • Pregnant or nursing (lactating) women and women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 3 months after stopping medication
Study treatment	• Brolucizumab 6 mg • Aflibercept 2 mg
Efficacy assessments	• BCVA • Spectral domain optical coherence tomography [redacted] • Color fundus photography • Fluorescein angiography
Key safety assessments	• Ophthalmic examination (IOP, slit-lamp, and fundus exam) • Fundus autofluorescence • Color Fundus Photography (preferably wide-field or with peripheral sweeps) • Post-injection assessment • Treatment emergent AEs, including AEs of special interest
Other assessments	[redacted] • Vascular Endothelial Growth Factor (VEGF)
Data analysis	**Primary analysis data set:** The primary efficacy analysis will be performed using FAS. The primary presentation of efficacy results will use Last-Observation-Carried-Forward (LOCF) approach for the imputation of missing values. All non-missing post-Baseline values including assessments done at unscheduled visits will be used when implementing the LOCF imputation. Baseline values will not be carried forward.

[redacted]

	Primary endpoint: The primary endpoint is the change in BCVA from Baseline to Week 52 or the last BCVA obtained before discontinuation from the study, whichever occurs first. **Primary statistical method:** Difference in means (brolucizumab q4 week dosing minus aflibercept q4 week dosing), calculated based on analysis of variance (ANOVA) model with the primary efficacy endpoint as the response variable, treatment, Baseline BCVA categories (<=70 >=71 letters), immediate prior treatment (aflibercept or ranibizumab) and time since first anti-VEGF injection (≤36 months, >36 months), and age categories (<75, >=75 years) as factors and its two-sided 95% confidence interval (CI) will be calculated for the primary efficacy analysis. Baseline BCVA is defined as the last measurement on or prior to Baseline visit. A non-inferiority of brolucizumab 6 mg dosed every 4 weeks to aflibercept 2 mg dosed every 4 weeks will be established if the lower limit of the 95 % CI mentioned above is greater than -4 letters (corresponding to the non-inferiority margin of 4 letters). **Sample size justification:** The primary efficacy variable is change in BCVA from Baseline. The primary analysis time point is Week 52. As suggested by the US regulatory authority, a non-inferiority margin of 4 letters is considered a clinically acceptable difference of brolucizumab 6 mg dosed every 4 weeks compared to aflibercept 2 mg dosed every 4 weeks in a previously treated population and will be utilized in this study. In SAVE study (Brown 2013) of ranibizumab (n=87), a standard deviation of 6.4 letters for the change in BCVA from Baseline was observed at Month 3. In ASSESS study (Singh 2015) (n=26), a standard deviation of 9.2 letters was obtained at Month 12. In this study, a standard deviation of 10 letters for the change in BCVA from Baseline to Week 52 in pre-treated patients is assumed. To meet US regulatory authority recommendation for safety assessment, data for brolucizumab 6 mg dosed every 4 weeks from at least 300 subjects with 12-month exposure are required. Thus, 450 subjects will be needed with a 2:1 ratio to brolucizumab 6 mg q4 weeks (300 subjects) and aflibercept 2 mg q4 weeks (150 subjects). This sample size is sufficient to demonstrate non-inferiority (margin = 4 letters) of brolucizumab 6 mg q4 weeks versus aflibercept 2 mg q4 weeks with respect to BCVA change from Baseline to Week 52 at a two-sided alpha level of 0.05 with a power of approximately 97% assuming equal efficacy and a common standard deviation of 10 letters. To account for a dropout rate of 12%, a total of 513 subjects (342 subjects to the brolucizumab 6 mg q4w arm and 171 to the aflibercept 2 mg q4w arm) will be randomized. The nQuery Advisor 7.0 was used for the above sample size calculations.
Key words	Neovascular age-related macular degeneration; nAMD; intravitreal injection; IVT; anti-VEGF; brolucizumab; aflibercept; EYLEA; double-masked; MERLIN

[redacted]

1 Introduction

1.1 Background

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

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

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

Brolucizumab (RTH258, formerly known as ESBA1008), is a humanized single-chain variable fragment (scFv) inhibitor of VEGF 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. Brolucizumab is designed for ophthalmic use and is administered by IVT injection. In this setting, the smaller molecular size of the scFv is expected to have advantages over IgG antibodies and larger antibody fragments due to the delivery of a higher molar dose (i.e. VEGF binding equivalents per mg protein), which may prolong the therapeutic effect and enable better tissue penetration at the retina.

In two large phase 3 pivotal studies (CRTH258A2301 [HAWK] and CRTH258A2302 [HARRIER]), brolucizumab was non-inferior to aflibercept in best-corrected visual acuity (BCVA) change from Baseline at Week 48, with over half the subjects in the brolucizumab arm maintained exclusively on a q12 week dosing interval after 3 monthly (i.e. every 4 weeks) loading doses. Safety was comparable between the treatment arms.

[redacted]

In nAMD, there is well known individual variability in clinical response to anti-VEGF agents-underlying factors including genetics, VEGF expression, lesion size, type and maturity may influence treatment response and frequency (Muether 2013, Stewart 2015).

In the United States, the Food and Drug Administration has approved monthly and pro re nata (prn) dosing regimens for aflibercept and ranibizumab for the treatment of nAMD, which provides flexibility to treat patients according to their individual needs.

Retina specialists strive to individualize treatment strategies to prevent CNV recurrence; however, currently the causes of variability in anti-VEGF treatment need in nAMD patients are not well understood, nor is there an accepted biomarker to identify the required anti-VEGF treatment frequency in individual patients. Despite attempts to maximize and individualize therapy, retinal fluid may persist, potentially limiting visual outcomes (Wykoff 2014, Jaffe 2016). In the pivotal studies of aflibercept, 28 – 36 % of subjects receiving bi-monthly aflibercept injections demonstrated residual intra-retinal edema (IRE) and/or sub-retinal fluid (SRF) following one year of treatment (Heier 2012). A post-hoc analysis of the VIEW data set showed that monthly dosing with aflibercept led to better fluid resolution in all compartments (Waldstein 2016) and in those subjects with early persistent fluid, monthly dosing of aflibercept led to improved BCVA gains at one year (Jaffe 2016).

In the two phase 3 studies of brolucizumab in treatment-naïve patients with nAMD, 8 weeks after the loading phase (i.e. Week 16) 30 % and 34 % of brolucizumab subjects had SRF/intra-retinal fluid (IRF) present compared to 45 % and 52 % of subjects in the aflibercept arm. By Week 48, following a q12/q8 week dosing regimen, 26 % and 31 % of brolucizumab subjects continued to have retinal fluid compared to 44 % and 45 % of q8 week aflibercept-treated subjects. These data suggest that a subset of patients may achieve additional visual acuity gains combined with further fluid resolution with more frequent dosing of brolucizumab.

Since the first marketing authorization approval of brolucizumab in October 2019 for the treatment of nAMD, adverse events of retinal vasculitis and/or retinal vascular occlusion, that my result in severe vision loss and typically in the presence of intraocular inflammation, have been reported from post-marketing experience with brolucizumab (Beovu). Considering these events, the overall risk/benefit assessment remains positive.

1.2 Purpose

Brolucizumab has not been studied in a long-term dosing regimen more frequently than every 8 weeks in patients with nAMD. Data related to a q4w dosing frequency is limited to a three-month loading phase.

This study will provide 104 -week data evaluating the safety and efficacy of a monthly (i.e. every 4 weeks) brolucizumab treatment regimen in prior-treated patients with nAMD as compared to monthly aflibercept. Patients to be enrolled into this study have recently shown response to anti-VEGF treatment while requiring frequent injections (e.g., on average every 4 – 5 weeks) to stabilize their CNV activity.

Subjects may be eligible to continue into an extension study in order to receive treatment with brolucizumab (a) after completing the 104 -week double-masked treatment period, (b) upon meeting all inclusion/exclusion criteria for the extension study, and (c) based on Investigator's

[redacted]

judgment that the subject is expected to benefit from treatment with brolucizumab. The objective of the extension study is to assess safety and efficacy of brolucizumab for an extended period.

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 evaluate whether brolucizumab 6 mg dosed every 4 weeks is non-inferior at Week 52 to aflibercept 2 mg dosed every 4 weeks	• Change in BCVA from Baseline to Week 52
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess efficacy of brolucizumab 6 mg dosed every 4 weeks compared with aflibercept 2 mg dosed every 4 weeks with respect to visual acuity (VA) stabilization or improvement at weeks 52 and 104 • To evaluate anatomic parameters of disease activity and retinal fluid status in patients treated with brolucizumab 6 mg dosed every 4 weeks compared with aflibercept 2 mg dosed every 4 weeks • To assess safety and tolerability of brolucizumab 6 mg dosed every 4 weeks compared with aflibercept 2 mg dosed every 4 weeks	*Efficacy Endpoints* • VA stabilization or improvement at Week 52 and Week 104 • Loss in BCVA of 5/10/15 letters or more from Baseline to post-baseline visit • Gain in BCVA of 5/10/15 letters or more from Baseline to post-baseline visit • Change in central subfield thickness (CST) from Baseline to post-baseline visit • Absence of IRF and/or SRF at post-baseline visit • Absence of sub-RPE fluid at post-baseline visit in patients with sub-RPE fluid at Baseline • Fluid free status- no IRF, SRF or sub-RPE fluid at post-baseline treatment visit • Time to first dry retina (no IRF or SRF) • Time to sustained dry retina (no IRF or SRF at ≥ 2 consecutive visits) *Additional Endpoints* [redacted] *Safety and Tolerability Endpoints* • Incidence of treatment-emergent Adverse Events (AEs) • Treatment-emergent changes in ocular and systemic parameters
[redacted]	[redacted]

[redacted]

Objective(s)	Endpoint(s)
[redacted]	

3 Study design

This is a multi-center, randomized, double-masked, parallel group study. This study has 2 masked arms where patients will be randomized with a 2:1 (brolucizumab:aflibercept) ratio.

All participants will have study visits every 4 weeks through Week 104 If a patient had discontinued in the first year (prior to week 52) they are not eligible to return into the study. The primary analysis of efficacy and safety data will be performed at Visit 14 (Week 52) (Figure 3-1).

Screening Period

Patients will be screened for enrollment into the double-masked treatment period at the Screening Visit. The screening period may last up to 14 days prior to administration of the first dose of study treatment, dependent upon confirmation of the patient meeting eligibility criteria.

Screening must occur between 21 and 31 days from the patient's last Standard of Care (SOC) anti-VEGF injection.

Including the Screening Period, the total study duration for a patient may be up to 106 weeks.

Double-Masked Treatment Period

Subjects meeting eligibility criteria will enter the treatment period and be randomized into one of the following 2 masked treatment arms at the Baseline visit:

Masked Arm 1: Brolucizumab 6 mg q4 weeks

Brolucizumab 6 mg will be injected every 4 weeks up to and including Visit 26 (Week 100).

Masked Arm 2: Aflibercept 2 mg q4 weeks

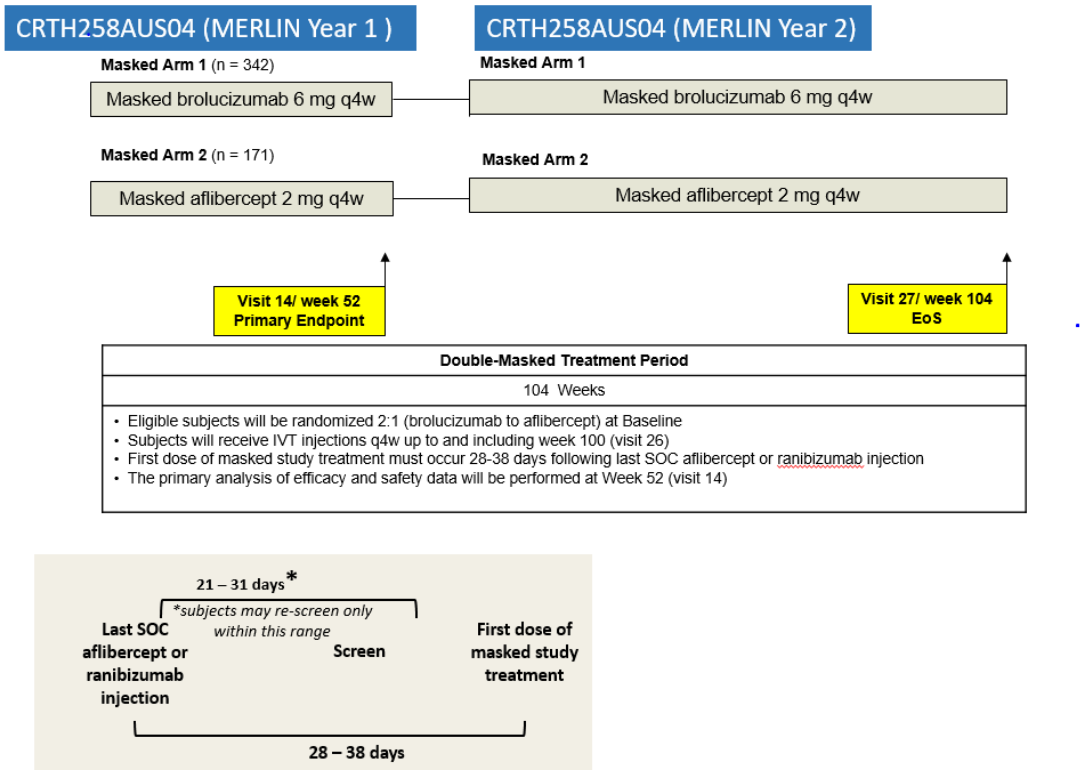
Aflibercept 2 mg will be injected every 4 weeks up to and including Visit 26 (Week 100).

The first dose of masked study treatment must be administered between 28 and 38 days from the subject's last SOC anti-VEGF injection.

The primary endpoint will be evaluated at~~,~~ Visit 14 (Week 52).

[redacted]

Figure 3-1 Study design



Subjects may be eligible to continue into an extension study in order to receive treatment with brolucizumab (a) after completing the 104 -week double-masked treatment period, (b) upon meeting all inclusion/exclusion criteria for the extension study, and (c) based on Investigator's judgment that the subject is expected to benefit from treatment with brolucizumab. The objective of the extension study is to assess safety and efficacy of brolucizumab for an extended period.

4 Rationale

4.1 Rationale for study design

This multicenter study is designed to evaluate whether brolucizumab 6 mg dosed every 4 weeks is safe and effective in nAMD patients with persistent fluid. To support efficacy assessments, anatomic parameters of disease activity and retinal fluid status change from Baseline will be evaluated. [redacted]

The inclusion criteria aim to identify a population of patients diagnosed with nAMD that have received recent, frequent anti-VEGF injections with a positive response to treatment and have

[redacted]

residual intra- and/or sub-retinal fluid. In order to demonstrate potential clinical benefit of more frequent dosing, patients with good vision will be included; this patient population has not been previously studied with brolucizumab and is described in more detail in Section 5 below.

4.2 Rationale for dose/regimen and duration of treatment

While there is well known variability in treatment need amongst nAMD patients, the underlying causes are unknown and there is no accepted biomarker to identify the required anti-VEGF treatment frequency in individual patients. Monthly dosing of aflibercept has been shown to improve fluid resolution and BCVA gains compared to bi-monthly dosing in a subgroup of nAMD patients with persistent retinal fluid (Jaffe 2016).

Analysis of data up to Week 96 from the CRTH258A2301 and CRTH258A2302 studies demonstrated non-inferiority in BCVA for brolucizumab 6 mg dosed q12/q8 weeks compared to aflibercept dosed q8 weeks in naïve nAMD patients. The current study will evaluate whether brolucizumab 6 mg dosed every 4 weeks is non-inferior to aflibercept 2 mg dosed every 4 weeks in change in BCVA in patients with retinal fluid despite frequent anti-VEGF injections.

A data gap exists in understanding the long term impact of monthly treatment in patients with persistent retinal fluid. Increasing the study duration to 104 weeks will generate supporting efficacy and safety data for an extended period for brolucizumab 6 mg dosed q4 weeks compared to aflibercept 2 mg dosed q4 weeks in patients with nAMD and persistent retinal fluid.

The primary analysis of efficacy and safety data will be performed at Week 52 (visit 14) In a study of monthly aflibercept, BCVA gains have been observed from Week 12 to Week 52, indicating that an efficacy assessment may be made at this time-point (Jaffe 2016).

4.3 Rationale for choice of comparator

Aflibercept 2 mg is an established standard of care option in treatment of nAMD and has been chosen as comparator for this study due to the approved dose and posology of aflibercept (EYLEA®) in the US for the targeted indication.

4.4 Purpose and timing of interim analyses/design adaptations

There will be one interim analysis after the last patient completes his/her Week 52 (primary analysis time point) visit.

The presentation of tables, listings, and figures will include data up to patients' date of Week 52 visit (inclusive). For adverse events and concomitant medications, Week 52 data including 30 days after patients' last IP administration at Week 48 will be included. All available data for patients discontinuing the study prior to Week 52 will be included in the interim analysis.

This interim analysis will be the primary analysis. There will be no hypothesis testing at Week 104. Therefore, no adjustment of the statistical significant level will be made for the primary hypothesis testing at Week 52.

[redacted]

4.5 Risks and benefits

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

Analysis of data up to Week 48 from the CRTH258A2301 and CRTH258A2302 studies demonstrated non-inferiority in BCVA for brolucizumab dosed q12/q8 weeks compared to aflibercept in naïve nAMD patients. Ocular and non-ocular (systemic) adverse events were comparable between the two groups.

Patients in both treatment groups experienced robust visual gains; however, there may be a subgroup of patients that require more frequent anti-VEGF injections and would benefit clinically from a monthly (q4 week) dosing schedule of brolucizumab. This effect has also been seen in the analyses of aflibercept studies, specifically in patients with unresolved fluid. Monthly dosing of aflibercept in this sub-population improved both BCVA and anatomical endpoints compared to q8 week aflibercept. Monthly treatment with brolucizumab may provide similar benefit.

There is an unmet medical need for patients with remaining retinal fluid despite a q8 week brolucizumab treatment regimen. Brolucizumab has not been studied in a dosing regimen more frequently than every 8 weeks in patients with nAMD. This study will evaluate whether brolucizumab 6 mg dosed every 4 weeks is non-inferior (as measured by BCVA gains) to aflibercept 2 mg dosed every 4 weeks.

Women of childbearing 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 outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

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

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.

5 Population

The study population will consist of male and female patients. Approximately 860 patients are expected to be screened with 513 patients to be randomized at approximately 66 sites in the United States. Patients who will consent will be extended in the study to continue until 104 weeks. If a patient had discontinued in the first year (prior to week 52) they are not eligible to return to the study.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study
2. Subjects must be 50 years of age or older at Screening

[redacted]

3. Active CNV lesions secondary to AMD that affect the central subfield (including retinal angiomatous proliferation [RAP] lesions with a CNV component) and which has associated IRF or SRF within the central 3 mm subfield in the study eye, confirmed by the Central Reading Center (CRC) at Screening
4. Total area of CNV (including both classic and occult components) must comprise > 50 % of the total lesion area in the study eye, confirmed by CRC at Screening
5. Received first anti-VEGF injection for nAMD in the study eye a minimum of 9 months prior to Screening
6. If first anti-VEGF injection for nAMD in the study eye received ≤ 36 months prior to Screening: BCVA ≥ 55 letters (approximate Snellen equivalent 20/80), inclusive, in the study eye at Screening and Baseline using Early Treatment Diabetic Retinopathy Study (ETDRS) testing; If first anti-VEGF injection for nAMD in the study eye received > 36 months prior to Screening: BCVA ≥ 65 letters (approximate Snellen equivalent 20/50), in the study eye at Screening and Baseline using ETDRS testing
7. Received at least 7 anti-VEGF injections in immediate prior 9 months; with the last two injections having been licensed anti-VEGF (aflibercept or ranibizumab)
8. Demonstrated nAMD fluid improvement or partial response with anti-VEGF therapy as determined by Investigator
9. Patients must have persistent IRF and/or SRF at Screening and Baseline as determined by Investigator

5.2 Exclusion criteria

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

1. Any active intra-ocular or peri-ocular infection or active intra-ocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis) in either eye at Screening and Baseline
2. Total area of fibrosis ≥ 50 % of the total lesion in the study eye, confirmed by CRC at Screening
3. Fovea of the study eye must not be affected by sub-retinal fibrosis or geographic atrophy by clinical exam and Optical Coherence Tomography (OCT), confirmed by CRC at Screening
4. Sub-retinal blood affecting the foveal center point and/or ≥ 50 % of the lesion of the study eye, confirmed by CRC at Screening
5. Any history or evidence of a concurrent intra-ocular condition in the study eye, including retinal diseases other than nAMD, that, in the judgment of the Investigator, could either 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)
6. Any current or history of macular or retinal disease other than wet AMD provided they reduce visual acuity or may confound assessment of the macula (e.g. diabetic macular edema (DME), retinal vein occlusion (RVO), pathologic myopia, uveitis, angioid streaks, ocular histoplasmosis, retinal detachment, epiretinal membrane that induces retinal striae

[redacted]

within 1 mm of the foveal center, macular hole, central serous chorioretinopathy, polypoidal vasculopathy)

7. RPE rip/tear in the study eye at Screening or Baseline
8. Current vitreous hemorrhage that limits visualization of the fundus or potential for visual acuity improvement in the opinion of the Investigator
9. History or evidence of the following in the study eye*:
   a. Intra-ocular or refractive surgery within the 90 day period prior to Screening
   b. Previous penetrating keratoplasty, vitrectomy or ocular radiation
   c. Previous panretinal photocoagulation
   d. Previous treatment with verteporfin photodynamic therapy
   e. Previous submacular surgery, other surgical intervention or laser treatment for AMD
   f. Uncontrolled glaucoma defined as intra-ocular pressure (IOP) >25 mmHg on medication or according to Investigator's judgment at Screening or Baseline
   g. Aphakia and/or absence of the posterior capsule at Screening or Baseline Yttrium Aluminum Garnet (YAG) laser posterior capsulotomy secondary to uncomplicated cataract extraction with posterior introccular lens implantation is allowed when >30 days from screening
   h. Intra- or peri-ocular use of corticosteroids during the 6 month period prior to Baseline
   i. Use of topical ocular corticosteroids for 30 or more consecutive days within the 90 day period prior to Screening

   Note: concomitant treatment with brolucizumab in the fellow eye during the study is prohibited

   *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.
10. Use of systemic corticosteroids for 30 or more consecutive days within 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); Inhaled, nasal or dermal steroids are permitted
11. 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 IP
12. History of hypersensitivity to any component of the test article or control article, or clinically relevant sensitivity to fluorescein dye as assessed by the Investigator
13. Participation in an investigational drug, biologic, or device study within 30 days or the duration of 5 half-lives of the IP (whichever is longer) prior to first dose

    Note: observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary
14. Systemic anti-VEGF therapy within the 90 day period prior to Screening
15. Stroke or myocardial infarction in the 90 day period prior to Screening
16. Uncontrolled blood pressure defined as a systolic value ≥160 mmHg or diastolic value ≥100 mmHg at Screening

[redacted]

17. Pregnant or nursing (lactating) women and women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 3 months after stopping medication. Highly effective contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject); Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment; In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
    c. Male sterilization (at least 6 months prior to Screening); For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    d. Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or 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 study treatment.

Women are considered post-menopausal and not of childbearing 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 childbearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the informed consent form (ICF).

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drugs

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Brolucizumab 6 mg/0.05 mL	Solution for injection	Intravitreal use	Masked; vials/or PFS	Sponsor local

Aflibercept 2 mg/0.05 mL	Solution for injection	Intravitreal use	Masked; vials/or PFS	Sponsor local

Brolucizumab is formulated as a sterile solution aseptically filled in a sterile glass vial for single-use and the content of the vial must **not** be split.

Brolucizumab study kits will be provided as a masked, numbered carton that contains 1 single-use, sterile glass vial containing brolucizumab 6 mg/0.05 mL or may be provided as a prefilled syringe (PFS) containing brolucizumab 6 mg/0.05 mL. Aflibercept study kits will be provided as a masked, numbered carton that contains one single use sterile glass vial or as a prefilled syringe (PFS) (subjected to appropriate regulatory update/approval) containing aflibercept 2 mg/0.05mL in its commercial presentation and one post-injection label containing the same kit number as the carton. The post-injection label will be placed on the aflibercept vial after use. Novartis will provide sufficient supplies of brolucizumab and aflibercept for treatment use to allow for completion of the study.

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/groups

Subjects completing the Screening period and meeting eligibility criteria will enter the treatment period and be randomized to one of the following 2 masked treatment arms/groups in a ratio of 2:1, respectively, at the Baseline (BL) (Visit 1/Week 0) visit.

- **Masked Arm 1: Brolucizumab 6 mg q4 weeks** – Brolucizumab 6 mg will be injected every 4 weeks up to and including Visit 26 (Week 100).
- **Masked Arm 2: Aflibercept 2 mg q4 weeks** – Aflibercept 2 mg will be injected every 4 weeks up to and including Visit 26 (Week 100).

The first dose of masked study treatment must be administered between 28 and 38 days from the subject's last SOC anti-VEGF injection.

6.1.4 Treatment duration

The planned total duration of study treatment is up to 104 weeks. 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 subject. For subjects who in the opinion of the Investigator are still deriving clinical benefit from study treatment, every effort will be made to continue provision of study treatment.

At the end of the study, subjects may be eligible to continue into an extension study in order to receive treatment with brolucizumab.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

The Investigator must instruct the subject to notify the study site about any new medications

[redacted]

he/she takes after the subject enrolled into the study.
All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate Case Report Forms (CRFs).

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

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed after the start of the study treatment. Medications known to be toxic to the lens, retina or optic nerve, including ethambutol, chloroquine/hydroxychloroquine, deferoxamine, phenothiazines and tamoxifen (except temporary use for COVID-19 treatment).

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Study eye		
Anti-VEGF therapy (licensed, unlicensed or investigational) other than IP (masked brolucizumab or aflibercept)	Any time	Discontinue study treatment
Intra-ocular or peri-ocular injections of corticosteroids (except if treatment for AE)	Any time	Discontinue study treatment (except if for treatment of AE)
Laser treatment for AMD Fellow eye	Any time	Discontinue study treatment
Investigational treatment; Avastin® is permitted	Any time	None
Brolucizumab treatment	Any time	Discontinue study treatment
Systemic		
Systemic corticosteroids for 30 or more consecutive days (low stable doses of corticosteroids [defined as ≤10 mg prednisolone or equivalent dose], inhaled, nasal, or dermal steroids are permitted)	Any time	Discontinue study treatment
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
Medications known to be toxic to the lens, retina or optic nerve, including ethambutol, chloroquine/ hydroxychloroquine,deferoxamine, phenothiazines and tamoxifen	Any time (except temporary use for COVID-19 treatment	Discontinue study treatment

[redacted]

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

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 subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The seven digit Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential (three digit) subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available by the Novartis EDC system. Once assigned to a patient, the Patient Number will not be reused. Patients who consent to continue in the study will continue to use the same number. The unmasked Investigator or his/her unmasked delegate will contact the IRT system and provide the requested identifying information for the patient to register them into the IRT.

If the patient fails to be treated for any reason, the unmasked Investigator or his/her unmasked delegate will notify IRT of the failure to treat. The reason for not being treated will need to be entered on the Screening Study Disposition eCRF.

6.3.2 Treatment assignment, randomization

Interactive Response Technology (IRT) will be used by the unmasked Investigator or his/her unmasked delegate for dispensing medication during the treatment period.

During the treatment period, eligible subjects will be randomized via IRT to one of the masked treatment arms, in a ratio of 2:1 (brolucizumab:aflibercept) at Visit 1 (Week 0/Baseline). Stratified randomization of subjects based on their most recent anti-VEGF treatment (aflibercept or ranibizumab) and time since first anti-VEGF injection in the study eye ($\leq$ 36 months prior to Screening or $>$ 36 months prior to Screening) will be performed using a centralized randomization schedule.

For randomization, the unmasked Investigator or his/her unmasked delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject based on the stratum the subject belongs to, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and masked investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility

[redacted]

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 subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment masking

This is a double-masked study, with subjects randomized to be treated with brolucizumab 6 mg q4w or aflibercept 2 mg q4w. The following individuals/groups will be masked to treatment assignment while the study is in progress:

- Subjects
- Investigators (i.e. the masked evaluating physician)
- Site staff (except for the unmasked site personnel and unmasked injecting physician)
- Sponsor/Contract Research Organization (CRO) clinical study team (except for those delegated with the responsibility of working with study drug and treatment code assignment)
- Sponsor/CRO clinical site management (except for those delegated with the responsibility of working with the study drug)
- Statisticians and clinicians directly involved in the conduct of the study (i.e. involved in patient level discussions or direct interaction with sites)

The following methods will be followed to maintain masking:

- Sponsor/CRO personnel who have access to treatment codes (e.g., unmasked Programming personnel directly involved in bioanalysis of serum samples, unmasked monitors performing study drug accountability, Clinical Supplies personnel) will not divulge the codes to subjects, investigators, site staff, Sponsor/CRO Clinical Trial Management (CTM) or Sponsor/CRO Clinical Site Management (CSM)
- Treatment allocation data will be kept strictly confidential until the time of unmasking and will not be accessible by anyone else involved in the study
- Study drug injections will be performed by an unmasked injecting physician
- Study drug preparation and administration will be concealed from subject and masked clinical site personnel view

To maintain the masking and data integrity at least two investigators (and corresponding study staff) will be involved in the study at each site: one masked (evaluating) investigator performing all assessments and capturing data in the electronic data capture (EDC) tool and one unmasked (treating) investigator administering study treatment according to the protocol. If a masked Investigator/ site personnel must change their role in the study to an unmasked role, then they must maintain the unmasked role from that point forward throughout the duration of the study.

The **Masked Investigator** is the evaluating physician responsible for all aspects of the study, excluding study drug administration and post-injection safety assessments. The masked investigator is masked to the treatment assignment and performs the monthly clinical assessments. Other site staff involved in performing study assessments and procedures (e.g.

[redacted]

BCVA, ophthalmic examination, disease activity assessments, upload of data in CRF) must also be masked to the treatment assignment. Masked study personnel must not be involved with study drug dispensation, preparation, or administration or post-injection safety assessments, which will be performed by unmasked study personnel only (see below). Masked Coordinators can complete the daily temperature logs, however, documentation will be required from the site on their specific process/plan for if/when a temperature excursion is noted and how the unmasked team members will be notified and timing of reporting.

The **Unmasked Investigator** is the treating physician and must not be involved with any aspects of the study other than study drug dispensation, preparation, or administration and post-injection safety assessments. The unmasked investigator performs the injections and will be unmasked to the treatments, as will any other site personnel who have been delegated responsibility of working with the study drug. The unmasked physician and other unmasked site personnel must not perform any other roles during the study except for the assessment of safety immediately following IVT injection. Unmasked site personnel can perform the lab draws as long as the blind is maintained. Post-injection safety assessment findings and any Adverse Events (AEs) observed by the unmasked investigator will be recorded in subject source documents for masked site personnel to enter into the appropriate CRFs.

Unmasked study personnel must not divulge the subject treatment assignment to anyone (masked site personnel, the subject and the masked Sponsor representative). Once the designated roles are determined, the roles cannot be switched at any time during the conduct of the study. Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this masked study.

Visual Acuity examiner (masked to the treatment assignment)

A Novartis-designated Visual Acuity (VA) Certifier will certify select site clinical staff with optometrical training to perform masked VA assessments for the purposes of this study. The VA examiner is masked to treatment assignment and will not perform any tasks that may unmask him or her to subject's treatment.

The detailed list of study tasks performed by masked and unmasked investigators and site personnel is provided in the Site Operations Manual (SOM)/Operational Manual.

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

Unmasking will only occur in the case of subject emergencies (Section 6.6.2) and at the conclusion of the study.

6.5 Dose escalation and dose modification

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

[redacted]

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 recorded in the CRF.

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.

[redacted]

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required 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 patient 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 patient whose treatment code has been broken for any reason. After an emergency break, the patient may still be eligible to continue in the extension study.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under Section 6.1.1.

[redacted]

A unique medication number is printed on the study medication label.

Unmasked Investigator staff will identify the study drug package(s) (medication kits) to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label). Immediately before dispensing the medication kit to the subject, unmasked site personnel will detach the outer part of the labelfrom the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

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 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 SOM/Operational Manual. 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.

To maintain treatment masking, IVT injections (both brolucizumab and aflibercept) must be prepared and administered by the unmasked treating physician (or unmasked site personnel delegated responsibility of working with the study drug) in a similar manner, away from subject and masked site personnel view. Details on study drug handling are outlined in the SOM/Operational Manual.

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

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

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

Double-Masked Treatment Period

Masked Arm 1: Brolucizumab 6 mg q4 weeks

Brolucizumab 6 mg will be administered via intravitreal injection (as described in the SOM/Operational Manual) every 4 weeks up to and including Visit 26 (Week 100) to subjects randomized to the brolucizumab 6 mg q4 week treatment arm.

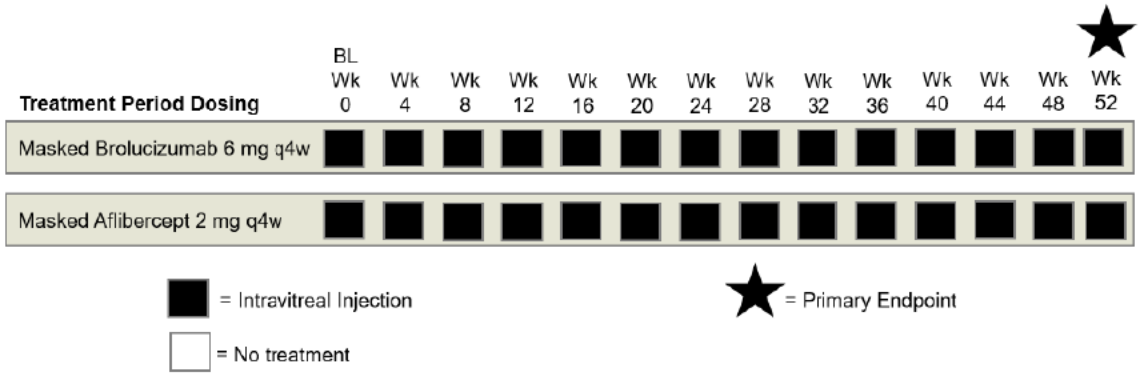
[redacted]

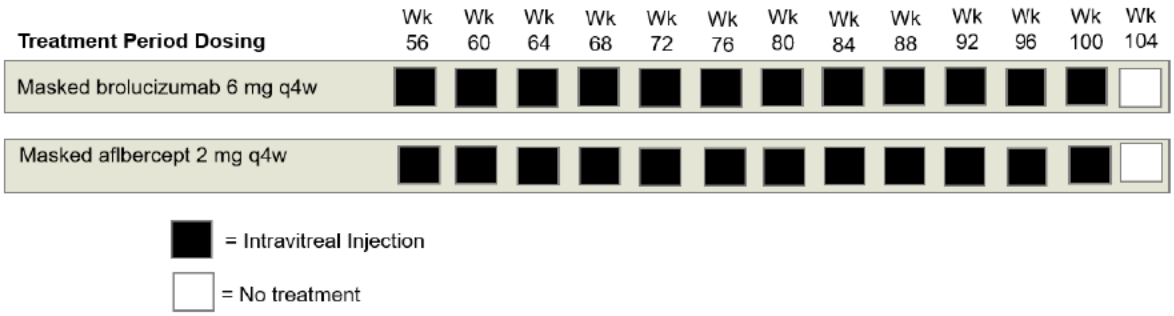
Masked Arm 2: Aflibercept 2 mg q4 weeks

Aflibercept 2 mg will be administered via intravitreal injection (as described in the SOM/Operational Manual) every 4 weeks up to and including Visit 26 (Week 100) to subjects randomized to the aflibercept 2 mg q4 week treatment arm.

The first dose of masked study treatment must be administered between 28 and 38 days from the subject's last SOC anti-VEGF injection.

Figure 6-1 Dosing schedule





Intravitreal injection

The IVT injection will be carried out under controlled, aseptic conditions per local clinical practice.

The study eye will be assessed before and after IVT 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 peri-ocular infections and in patients with active intra-ocular inflammation (IOI); therefore, the Investigator must verify that these conditions are not present in either eye (study or fellow 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 (Section 8.4).

If IOI confirmed, subjects should be treated for IOI according to clinical practice. In the event of active ocular or peri-ocular infections or intra-ocular inflammation, subjects may be re-evaluated at an unscheduled visit within 7 days to receive this protocol-defined visit injection. If not resolved within 7 days, the visit dosing will resume with the next scheduled visit.

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.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject 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 subject source documents.

As new information becomes available, informed consent will be updated and then must be discussed with the subject.

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 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. Novartis will provide to Investigators in a separate document a proposed informed consent form that complies with the International Conference on Harmonization (ICH) Good Clinical Practice (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 subject 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

[redacted]

safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of childbearing 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.

Subjects might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

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

8 Visit schedule and assessments

The assessment schedule (Table 8-1) lists all of the assessments and indicates with an "X" (or an "S" for source-only) 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 (EoS) 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. Additional ocular examination and imaging assessment may be conducted at unscheduled visits as per discretion of the Principal Investigator. If the COVID-19 pandemic limits or prevents on-site study visits, if study treatment could not be administered and/or if 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

Evaluation schedule:

Study Period	Screening													
Visit Name	**Screen Visit**	**V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**V10**	**V11**	**V12**	**V13**
Week	**-2 to 0**	**0 BL**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Visit window (days)	**Up to 14 days prior to BL**		**Day 28±7**	**Day 56±7**	**Day 84±7**	**Day 112±7**	**Day 140±7**	**Day 168±7**	**Day 196±7**	**Day 224±7**	**Day 252±7**	**Day 280±7**	**Day 308±7**	**Day 336±7**
Informed consent	X													
Demographics	X													
Medical History	X													
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Surgeries and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X	X												
General Physical Exam	S													
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and Weight	X													
Pregnancy Test, if applicable [a]	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Chemistry/ Hematology/ Urinalysis [b]	X				X									
Best-Corrected Visual Acuity (BCVA) [f] *([e] both eyes where indicated)*	X[e]	X[e]	X	X	X[e]	X	X	X[e]	X	X	X[e]	X	X	X
Complete Ophthalmic Exam [f] *([e] both eyes where indicated)*	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Spectral Domain Optical Coherence Tomography (SD-OCT) [redacted] *([e] both eyes where indicated)*	X[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus Photography (CFP) [f] *([e] both eyes where indicated)*	X[e]				X									

[redacted]

Study Period	**Screening**													
Visit Name	**Screen Visit**	**V 1**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9**	**V10**	**V11**	**V12**	**V13**
Week	**-2 to 0**	**0 BL**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Visit window (days)	**Up to 14 days prior to BL**		**Day 28±7**	**Day 56±7**	**Day 84±7**	**Day 112±7**	**Day 140±7**	**Day 168±7**	**Day 196±7**	**Day 224±7**	**Day 252±7**	**Day 280±7**	**Day 308±7**	**Day 336±7**
Fluorescein Angiography (FA) [f] (*[e] both eyes where indicated)*	X [e]				X									
Fundus Autofluorescence (FAF) [f] (*[e] both eyes where indicated)*		X [e]			X									
[redacted]														
Optional Trial Feedback Questionnaire		S						S						
Contact IRT	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Administer Study Injection/ Post-injection Assessment [c]		X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Study Period														
Visit Name	**V 14**	**V 15**	**V 16**	**V 17**	**V 18**	**V 19**	**V 20**	**V 21**	**V 22**	**V 23**	**V 24**	**V 25**	**V 26**	**Exit/ V27 [d]**
Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104 EoS**
Visit window (days)	**Day 364±7**	**Day 392±7**	**Day 420±7**	**Day 448±7**	**Day 476±7**	**Day 504±7**	**Day 532±7**	**Day 560±7**	**Day 588±7**	**Day 616±7**	**Day 644±7**	**Day 672±7**	**Day 700±7**	**Day 728±7**
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Surgeries and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test, if applicable [a]	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Chemistry/ Hematology/ Urinalysis [b]	X			X										X
Best-Corrected Visual Acuity (BCVA) [f] *([e] both eyes where indicated)*	X [e]	X	X	X [e]	X	X	X [e]	X	X	X [e]	X	X	X	X [e]
Complete Ophthalmic Exam [f] ([e] both eyes where indicated)	X [e]	X	X	X	X	X	X	X	X	X	X	X	X	X [e]
Spectral Domain Optical Coherence Tomography (SD-OCT); [redacted] *([e] both eyes where indicated)*	X [e]	X	X	X	X	X	X	X	X	X	X	X	X	X [e]
Color Fundus Photography (CFP) [f] ([e] both eyes where indicated)	X [e]			X										X [e]
Fluorescein Angiography (FA) [f] ([e] both eyes where indicated)	X [e]			X										X [e]
Fundus Autofluorescence (FAF) [f] ([e] both eyes where indicated)	X [e]			X										X [e]

[redacted]

Study Period														
Visit Name	**V 14**	**V 15**	**V 16**	**V 17**	**V 18**	**V 19**	**V 20**	**V 21**	**V 22**	**V 23**	**V 24**	**V 25**	**V 26**	**Exit/ V27 [d]**
Week	**52**	**56**	**60**	**64**	**68**	**72**	**76**	**80**	**84**	**88**	**92**	**96**	**100**	**104 EoS**
Visit window (days)	**Day 364±7**	**Day 392±7**	**Day 420±7**	**Day 448±7**	**Day 476±7**	**Day 504±7**	**Day 532±7**	**Day 560±7**	**Day 588±7**	**Day 616±7**	**Day 644±7**	**Day 672±7**	**Day 700±7**	**Day 728±7**
[redacted]														
Optional Trial Feedback Questionnaire	S						S							S
Contact IRT	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Administer Study Injection/ Post-injection Assessment [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	

a– Women of childbearing potential only. Urine pregnancy tests will be performed unless local regulations require a serum pregnancy test
b – All blood draws should be performed prior to receiving the IVT injection
c – The study eye will be evaluated within 5 minutes and approximately 30 minutes post injection to ensure that the injection procedure and/or the investigational product have not endangered the health of the eye
d – All procedures should be followed, regardless of when the patient exits the study
e– Both eyes; all other assessments are study eye only
f- Additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation. Wide Field FA Imaging in the event of Intraocular Inflammation (IOI).

8.1 Screening

Screening must occur between 21 and 31 days from the patient's last SOC anti-VEGF injection (either aflibercept or ranibizumab).

The completion of assessments for this visit may occur on different days. The screening period starts with the first screening procedure (other than signing of the ICF).

One time re-screening of subjects will be allowed in the following circumstances:

1. laboratory test(s), BCVA, or imaging assessments need to be repeated; or
2. when a subject has a temporary medical condition precluding participation

Subjects may re-screen with the other eye should the initial eye not qualify for entry into the study, under the condition that the subject re-screens within the 21 – 31 day window from patient's last SOC anti-VEGF injection for the new eye.

As long as laboratory tests, BCVA, or imaging assessments can be repeated (or temporary medical condition resolves) within 14 days of the first screening (and within 21 – 31 days from

[redacted]

patient's last SOC anti-VEGF injection), the other screening assessments as required for Screening per Table 8-1 do not need to be repeated. If re-screening is to occur beyond 14 days from the original screening visit date, then all screening procedures except Fluorescein Angiography (under the condition that the original FA images qualify the patient for entry into the study) must be repeated. Medical judgment should be exercised to ensure that treatment is not withheld in order for a subject to participate in the study. Subjects that do not qualify for entry into the study may continue to receive SOC injections prior to re-screening. Subjects may re-screen only within the 21 – 31 day window from patient's last SOC anti-VEGF injection.

Subjects eligible for re-screening are considered screen failures and will be re-screened under a new subject number. The screen failure must be recorded in both the CRF and IRT. For the re-screened subject, the original screening number (which is considered a screen failure) is entered on the subject re-screening CRF.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered a screen failure. The date of visit, screening phase disposition, subject re-screening (if applicable), and reason for screen failure (including withdrawal of informed consent) should be recorded on the appropriate CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (see Serious Adverse Event (SAE) Section 10.1.3 for reporting details). If the subject fails to be randomized, the IRT must be notified of the screen fail and that the subject was not randomized.

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

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include age, sex, race, ethnicity, Japanese ancestry, study eye, iris color, history of primary diagnosis, time since first anti-VEGF injection (≤ 36 months or > 36 months), and most recent anti-VEGF treatment (aflibercept or ranibizumab).

Additionally, the following data will be collected for all subjects at Baseline: vital signs, BCVA, and concomitant medications.

8.3 Efficacy

Efficacy assessments will include BCVA with ETDRS-like chart at 4 meters, Spectral Domain Optical Coherence Tomography (SD-OCT), [redacted] color fundus photography, and Fluorescein Angiography (FA).

[redacted]

8.3.1 Best-Corrected Visual Acuity

The BCVA testing will be conducted in the study eye at every visit. The BCVA testing will be conducted in both eyes at Screening, Visit 1 (Week 0 [Baseline]), Visit 4 (Week 12), Visit 7 (Week 24), Visit 10 (Week 36), Visit 14 (Week 52) and Visit 27 (Week 104/EoS).

All BCVA testing should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye, or administration of study treatment.

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

If it is not possible to perform a subjective refraction or VA testing at 4 meters because VA is too poor for the subject to read at least 4 letters on the ETDRS chart at this distance, the refraction/VA testing should be attempted at 1 meter. Further details on refraction technique and VA testing will be described in a separate handbook.

Investigators and/or their designated study staff performing VA assessments as well as all the equipment will be certified for this trial by Novartis-designated VA certifiers.

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

8.3.2 Spectral Domain Optical Coherence Tomography

SD-OCT will be assessed in the study eye at every study visit and in both eyes at Screening, Visit 14 (Week 52) and Visit 27 (Week 104/EoS) only.

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

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

[redacted]

8.3.4 Color fundus photography

Color fundus photography will be assessed in both eyes at Screening, Visit 14 (Week 52) and Visit 27 (Week 104/EoS) and in the study eye only at Visit 4 (Week 12) and Visit 17 (Week 64). A standardized procedure for the collection of 3-field color fundus photographic images is provided by the CRC in a separate handbook. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects. At the Screening Visit, retinal images will be sent to the CRC for determination of eligibility. Feedback from the CRC following expedited review will be provided to the sites via email or fax.

8.3.5 Fluorescein Angiography

FA will be assessed in both eyes at Screening, Visit 14 (Week 52) and Visit 27 (Week 104/EoS) and in the study eye only at Visit 4 (Week 12) and Visit 17 (Week 64).

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

8.3.6 Appropriateness of efficacy assessments

BCVA, SD-OCT, [redacted] and FA are standard assessments for this indication and patient population, and well established in the field of ophthalmologic clinical research.

8.4 Safety/Tolerability

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, regular 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.

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

For details on AE collection and reporting, refer to Section 10.

Table 8-2 Assessments & specifications

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

[redacted]

Assessment	Specification
	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 recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent that meet the definition of an Adverse Event must be recorded as an adverse event.
Ophthalmic examination	The ophthalmic exam will be performed in the study eye at every study visit, and in both eyes at Screening, Visit 14 (Week 52) and at Visit 27 (Week 104/EoS). A complete description of standardized procedures and grading scales is outlined in the SOM/Operational Manual. If study visit assessments and a corresponding treatment occur on separate days, ophthalmic examinations should be performed as safety check-up before treatment of the eye. Additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation for safety evaluation. 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 arterial occlusion (RAO) is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and will conduct OCT (Section 8.3.2), fluorescein angiography (preferably wide-field or with peripheral sweeps) and color fundus photography (see Section 8.3.4). 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. The ophthalmic exam will consist of the following: **Slit-lamp examination (Biomicroscopy)** – includes evaluation of the anterior segment structures including eyelids/lashes, conjunctiva, anterior chamber, cornea, iris, lens, anterior part of the vitreous and aqueous reaction (cells and flare). This will be completed at every (scheduled and unscheduled) visit to examine the anterior segment structures of the study eye (fellow eye will be examined at screening, Visit 14 (Week 52), and Visit 27 (EoS) and at the discretion of the investigator). Slit lamp examination must be carefully performed before each study treatment. 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. The outcome of the examination will be recorded in the source documents (e.g., ophthalmic examination tool) and captured in the appropriate eCRF as applicable. Slit lamp examination must be carefully performed before each study treatment. If there are 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. **Intra-ocular pressure measurement** – a measurement of IOP will be conducted using an applanation tonometer or Tonopen. The same method should be used throughout the study for each subject.

[redacted]

Assessment	Specification
	Fundus exam – includes evaluation of the vitreous, retina, macula, choroid, and optic nerve. Dilation for the fundus exam is at the discretion of the Investigator.
Fundus Autofluorescence	Fundus Autofluorescence (FAF) will be performed to assess the occurrence of geographic atrophy. FAF will be performed in both eyes at Visit 1 (Week 0/BL), Visit 14 (Week 52), and Visit 27 (Week 104/EoS) in the study eye only at Visit 4 (Week 12) and Visit 17 (Week 64). A standardized procedure for the collection of FAF images is provided by the CRC in a separate handbook. Verification of the equipment and certification of examiners at each investigative site will occur prior to evaluation of study subjects. FAF images will not be used to determine eligibility.
Post-injection assessment	The study eye will be assessed immediately (0-5 minutes) after and 30 (± 15) minutes after each IVT injection to ensure that the procedure and/or the study medication have not endangered the health of the eye. The post-injection assessments include an evaluation of central retinal artery perfusion via a gross assessment of vision (e.g. count fingers) and measurement of IOP according to the schedule detailed in the SOM/Operational Manual. Direct visualization to assess the central retinal artery, presence of retinal detachment, presence of new intra-ocular hemorrhage(s) might be appropriate at the discretion of the Investigator and/or based on the results of gross assessment of vision and IOP measurement. Assessments will continue until the central retinal artery is adequately perfused and the IOP is within 10 mmHg of the pre-injection value and is stable in the opinion of the Investigator. Any subject who develops significantly raised IOP (> 30 mmHg) or a non-adequately perfused central retinal artery at any time during the study should be monitored according to the Investigator's clinical judgment and may undergo additional procedures and measurement of IOP beyond those specified in the protocol. If, at the conclusion of the required evaluation period following an injection, there are no safety concerns, the subject will leave the site. Intraocular pressure treatment and close monitoring of IOP should be performed by the investigator for any non-transient elevation in intraocular pressure (≥30 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 ≥30 mmHg, assessment should be repeated until back to normal. If any concern or immediate toxicity is noted, the subject will remain at the site and will be treated according to the designated evaluating physician's clinical judgment. If any issues regarding IOP are noted during the post-injection assessment, then the subject should be scheduled for a follow-up visit (Unscheduled Visit) the day following injection, if required in the opinion of the Investigator. Clinically relevant changes that are observed during the post-injection assessment should be reported as adverse events.
Vital signs	Vital signs include blood pressure (BP) and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using a mercury sphygmomanometer, an aneroid

[redacted]

Assessment	Specification
	manometer, an automated sphygmomanometer or a validated electronic device according to local practice. All equipment must be calibrated according to the manufacturer's recommendation and wherever possible the same type of device should be used for an individual subject throughout the study. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. On days when study drug is administered, vital signs will be measured before administration of study medication.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at Screening.
Treatment emergent AEs, including AEs of special interest	AEs will be coded using the MedDRA dictionary and presented by system organ class and preferred term. Treatment emergent AEs will be analyzed based on the number and percentage of subjects with at least one AE in the category of interest. An adverse event of special interest (ESI) is one of scientific and medical concern specific to the Sponsor's product or program where ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. ESI is subject to change during the course of study ESIs to be reported within 24 hours of the Investigator's or site's knowledge of the event include the following but is not limited to: • 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

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected at the visits indicated in Table 8-1. The results of the laboratory examinations should be recorded in the source documents only. Any clinically significant abnormalities will be recorded on the adverse event page of the CRF.

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

All blood draws and urine collections should be performed prior to receiving the IVT injection and prior to injection of fluorescein dye.

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

[redacted]

Table 8-3 Laboratory assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Red Blood Cell (RBC) count, White Blood Cell (WBC) count with Differential (absolute and percentage of Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Other), and quantitative Platelet count
Chemistry	Blood Urea Nitrogen (BUN) or Urea, Serum Creatinine, 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, Amylase, Lipase, Glucose (non-fasting), The following liver function tests (LFTs): Aspartate aminotransferase [AST (SGOT)], Alanine aminotransferase [ALT (SGPT)], Alkaline Phosphatase (ALP), Gamma-Glutamyl Transferase (GGT), total Bilirubin, direct Bilirubin, indirect Bilirubin, and Lactate Dehydrogenase (LDH)
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, pH, Protein, Specific Gravity, Nitrite, Leukocyte esterase, Urobilinogen) Reflex Microscopic Panel (RBCs, WBCs, Casts, Crystals, Bacteria, Mucus, Epithelial Cells)
Pregnancy Test	Serum / Urine pregnancy test (refer to Pregnancy Section 8.4.2)

8.4.2 Pregnancy and assessments of fertility

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

A urine pregnancy test will be conducted for all women of childbearing potential to assess pregnancy prior to administration of the first dose of study treatment (Screening Visit) at Visit 14 (Week 52) and at Visit 27 (Week 104/EoS). During the study, monthly urine pregnancy testing will be performed.

Assessments of Fertility

Assessments of fertility by follicle-stimulating hormone (FSH) testing at Screening will only be required in the event that medical documentation of follow-up hormone level assessment to confirm reproductive status in women that have had surgical bilateral oophorectomy without a hysterectomy is unavailable, as described in Section 5.2.

Should post-menopausal status not be confirmed, the patient will undergo pregnancy testing as indicated in Table 8-1 and agree to follow contraception requirements as indicated in Section 5.2.

8.4.3 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population. If there are any signs of IOI, additional assessment will be performed (Table 8-1).

[redacted]

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Trial Feedback

During the treatment period, subjects might be asked to complete an optional anonymized questionnaire, "Trial Feedback Questionnaire" to provide feedback on their clinical trial experience at Visit 1 (Week 0 [Baseline]), Visit 7 (Week 24), Visit 14 (Week 52) and Visit 27 (Week 104/EoS). Responses would not be reviewed by Investigators. Responses would be used by the sponsor (Novartis) to understand where improvements can be made in the clinical trial process. This questionnaire is not meant to collect data about the patient's disease, symptoms or adverse events and therefore would not be considered trial data. Should any spontaneous information be collected about AEs, this would be transferred to the safety database. Subjects may opt in or opt out of completing this questionnaire. Imaging SD-OCT, [redacted] color fundus photography, and FA imaging procedures will address efficacy objectives. FAF will be performed to address safety.

The methods for assessment and recording are specified in the handbook provided by the CRC.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a patient 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 must discontinue study treatment for a given subject if on balance; he/she believes that continuation would negatively impact the risk/benefit of trial participation. Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 8.4.2 and Section 10.1.4)
- Use of prohibited treatment as per recommendations in Section 6.2.2
- Any situation in which study participation might result in a safety risk to the patient
- Unsatisfactory therapeutic effect
- Patient's condition no longer requiring study treatment

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. 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.

The Investigator should encourage the subject to continue in the study and to return for the remaining visits up to and including Visit 14 (EoS). Otherwise, the subject should return to the clinic as soon as possible, after discontinuation of study drug, for an EoS visit. EoS visit assessments detailed in Table 8-1 should be completed and recorded in the CRF.

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 Unmasked team 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, emergency breaking of treatment code.

9.1.2 Withdrawal of informed consent

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

[redacted]

- Does not want to participate in the study anymore

Or

- Does not want further visits or assessment

Or

- Does not want any further study related contacts

Or

- Does not allow analysis of already obtained biologic material (does not apply if only related to genetic material)

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.

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, however the data collected during the period of participation in the study may be used.

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 patients will not be replaced.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient t 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.

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

[redacted]

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible 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 local regulation) will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their End of Study visit, 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.

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

Subjects may be eligible to continue into an extension study in order to receive treatment with brolucizumab (a) after completing the 104 -week double-masked treatment period, (b) upon meeting all inclusion/exclusion criteria for the extension study, and (c) based on Investigator's judgment that the subject is expected to benefit from treatment with brolucizumab.

The objective of the extension study is to collect further safety and efficacy data on brolucizumab

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. 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 subjects 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.

[redacted]

Adverse events must be recorded 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 or the ocular injection procedure
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved
4. whether it constitutes an SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding study treatment
6. for ocular AEs, the eye the AE occurred in

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

- No action taken (e.g. further observation only)
- Drug interrupted/withdrawn
- Concomitant medication or non-drug therapy given
- Patient hospitalized/patient's hospitalization prolonged (see Section 10.1.2 for definition of SAE)

7. its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; 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 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

[redacted]

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 that are considered to be non-typical in subjects with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

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

Life-threatening in the context of an 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 (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - 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 an 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 or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

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.

[redacted]

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 the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. 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 Chief Medical Office & Patient Safety (CMO&PS) Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an IN to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

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

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 should be recorded and reported by the Investigator to the Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment for any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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.

[redacted]

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF 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

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE CRF	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 Liver safety monitoring

To ensure subject safety and to ensure that a full data package is collected to best understand events of liver dysfunction that emerge during the course of this study, a standardized process for evaluation of liver events has to be followed. This may involve referral of the patient to a suitable internal medicine physician.

This additional investigation is triggered by liver function test abnormalities and/or adverse events (irrespective of whether classified/reported as AE/SAE and irrespective of Investigator suspected causality).

Please refer to Table 16-2 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory test abnormality trigger or liver event as defined in Table 16-2 should be followed up by the Investigator or designated personnel at the trial site or a suitable internal medicine physician as summarized below.

For the liver laboratory test abnormality trigger:

- If the elevation is confirmed as clinically significant, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate. This observation may be conducted by the Investigator or through referral of the patient to a suitable internal medicine physician.

For the liver adverse events, consider referral of the patient to a suitable internal medicine physician and the guidance below:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment Section 9.1.1, if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medication)

[redacted]

- An investigation of the liver event which needs to be followed until resolution
- If meeting SAE criteria, the event must be reported as per Section 10.1.3

All follow-up information, additional procedures performed and test results must be collected and documented at the study site.

10.2.2 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
  - confirmed (after ≥24h) increase in serum creatinine of ≥25% compared to Screen Visit during normal hydration status
- Urine event
  - new onset (≥1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Table 16-3 in Appendix 3 should be followed up by the Investigator or designated personnel at the trial site as summarized in Appendix 3.

For the renal adverse events, consider referral of the patient to a suitable internal medicine physician. All follow-up information, additional procedures performed and test results must be collected and documented at the study site.

11 Data collection and database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the CRFs. The CRFs 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 CRFs, and allow modification and/or verification of the entered data by the investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into CRF) 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.

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

[redacted]

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 (ATC) 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 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.

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. 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. CRFs) 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 GCP, 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 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, 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).

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

[redacted]

study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

11.4 Data Monitoring Committee

The RTH258 program level Data Monitoring Committee (DMC) will monitor overall safety. DMC will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study.

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.

12 Data analysis and statistical methods

The analysis will be conducted on all subject data at the time the trial ends.

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

Additional analysis may be considered to evaluate the impact of COVID-19 pandemic.

12.1 Analysis sets

The Randomized Analysis Set (RAS) consists of all randomized subjects. This analysis set will be used to describe the randomized subjects by treatment group with respect to demographics and Baseline characteristics.

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent-to-treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure. This analysis set will be used for all efficacy analyses.

The Per-Protocol Set (PPS) defined for the primary efficacy analysis at Week 52 includes all subjects in the FAS with no protocol deviations that are expected to majorly affect the assessment of efficacy at Week 52 including: lack of compliance (including treatment misallocation), missing data, concomitant medication and deviation from inclusion/exclusion criteria. Discontinuation from treatment due to lack of efficacy does not constitute a reason for exclusion from PPS.

The Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the first study treatment received if the randomized treatment was never received. All safety analyses will be based on the Safety Set.

There will be two separate statistical analyses; an interim analysis of 52 weeks data and a final analysis of 104 weeks data. The primary time point for analysis of efficacy and safety data is Week 52. Analysis at other time points will be considered as supportive or supplemental.

[redacted]

12.2 Subject demographics and other baseline characteristics

Demographic and other Baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the RAS, FAS, and Safety Set.

Categorical data will be presented as frequencies and percentages by treatment group. For continuous data, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, interquartile range, and maximum will be presented by treatment group.

Relevant medical histories and current medical conditions at Baseline will be summarized by system organ class and preferred term, by treatment group.

12.3 Treatments

The Safety Set will be used for the analyses described in this section. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, interquartile range, and maximum will be presented.

The duration of exposure (in days) to study medication will be summarized by means of descriptive statistics by treatment group.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the ATC classification system, by treatment group.

12.4 Analysis of the primary endpoint

The primary aim of the study is to evaluate whether brolucizumab 6 mg dosed every 4 weeks is non-inferior to aflibercept 2 mg dosed every 4 weeks based on BCVA assessment at Week 52.

12.4.1 Definition of primary endpoint

The change in BCVA from Baseline to Week 52 or the last BCVA obtained before discontinuation from the study, whichever occurs first.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary efficacy analysis will be performed using FAS. An analysis of variance (ANOVA) model with the primary efficacy endpoint as the response variable, and treatment, Baseline BCVA categories (<=70, >=71 letters), immediate prior treatment (aflibercept or ranibizumab) and time since first anti-VEGF injection (≤ 36 months, > 36 months), and age categories (<75, >=75 years) as factors will be used for the primary efficacy analysis

Difference in means (brolucizumab q4 week dosing minus aflibercept q4 week dosing) of the primary efficacy endpoint and its two-sided 95 % confidence interval (CI) will be calculated using the above-mentioned ANOVA model.

Baseline BCVA is defined as the last measurement on or prior to Baseline visit.

[redacted]

A non-inferiority of brolucizumab 6 mg dosed every 4 weeks to aflibercept 2 mg dosed every 4 weeks will be established if the lower limit of the 95 % CI mentioned above is greater than -4 letters (corresponding to the non-inferiority margin of 4 letters).

The hypothesis of non-inferiority will not be tested at Week 104. Thus, the primary non-inferiority test at Week 52 will be performed at 5% level of significance. Adjustment of level of significance for the primary analysis at Week 52 is not applicable.

12.4.3 Handling of missing values/censoring/discontinuations

The primary presentation of efficacy results will use Last-Observation-Carried-Forward (LOCF) approach for imputation of missing values. All non-missing post-Baseline values including assessments done at unscheduled visits will be used when implementing the LOCF imputation. Baseline values will not be carried forward.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses

A sensitivity analysis to explore impact of protocol deviations on the primary efficacy results at Week 52 will be performed using the PPS with LOCF imputation of missing values using the same model and factors as in the primary efficacy analysis model.

Another sensitivity analysis to explore the robustness of the primary efficacy analysis results related to missing values will be performed by using observed-case approach in the FAS. A repeated measures ANOVA model with the primary efficacy endpoint as the response variable, and treatment, week, treatment-by-week interaction, Baseline BCVA categories (<=55, 56-70, >=71 letters), prior treatment (aflibercept or ranibizumab) and time since first anti-VEGF injection (≤ 36 months, > 36 month), and age categories (<75, >=75 years) as factors will be employed. An unstructured covariance matrix for the repeated measures within each subject will be applied in the analysis. The two treatment groups will be compared at Week 52 by reporting a point estimate together with a 95% CI for the treatment difference, based on least squares means. The SAS® procedure PROC MIXED will be used for the above analyses.

Supportive analyses

The following potential subgroup analyses (to be expanded) of change in BCVA from Baseline to Week 52 will be performed as supportive analysis of the primary analysis at Week 52:

- Subjects with high fluid burden at Baseline as determined by CRC
- Subjects with Baseline BCVA 20/40 or worse
- Prior anti-VEGF treatment

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoints

The secondary efficacy endpoints are the following:

1. VA stabilization or improvement (no change or gain in BCVA compared to Baseline) (yes, no)

[redacted]

2. Gain of 15 letters of more in BCVA (yes, no)
3. Gain of 10 letters of more in BCVA (yes, no)
4. Gain of 5 letters of more in BCVA (yes, no)
5. Loss of 5 letters of more in BCVA (yes, no)
6. Loss of 10 letters of more in BCVA (yes, no)
7. Loss of 15 letters of more in BCVA (yes, no)
8. Change in Central Subfield Thickness (CST) from Baseline to each post-Baseline visit
9. IRF (present, absent)
10. SRF (present, absent)
11. Sub-RPE fluid (present, absent)
12. Fluid free (no IRF, SRF or sub RPE fluid) status (yes, no)
13. Time to first dry retina (no IRF or SRF) finding
14. Time to first sustained dry retina (no IRF or SRF at ≥ 2 consecutive visits) finding

Categorical Variables 1 to 7 and 9 to 12 will be summarized descriptively by treatment and visit. Difference in proportions, brolucizumab q4 week dosing – aflibercept q4 week dosing, and its two-sided 95% CI will be calculated using normal approximation method.

Continuous Variable 8 will be analyzed in a similar method as used in the analysis of primary efficacy variable by visit.

Time-to-event Variables 13 and 14 will be analyzed using Kaplan-Meier method. Proportions of patients with event will be presented by treatment group and time point, together with standard errors (using Greenwood's formula). At each time point, the difference in the proportion of patients with event between the treatment groups will be presented using the test statistic for the large sample test of equality of two treatment groups, corresponding standard error, 95% CI, and p-value (Lachin 2000).

12.5.2 Safety endpoints

For all safety analyses, the Safety Set will be used. All listings and summary tables will be presented by treatment group

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of Baseline data, which will also be summarized where appropriate (e.g. change from Baseline summaries). In addition, a separate listing for death including on-treatment and post-treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to the last study visit.

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication, or events present prior to start of double-masked

[redacted]

treatment but increased in severity based on preferred term) will be summarized in the following ways:

- By treatment, primary system organ class and preferred term.
- By treatment, primary system organ class, preferred term and maximum severity.
- By treatment, pre-defined topic of interest, primary system organ class and preferred term.

Separate summaries will be provided for study medication related adverse events, serious adverse events, and other significant adverse events leading to discontinuation.

The number (and proportion) of subjects with adverse events of special interest will be summarized by treatment, primary system organ class and preferred term.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Adverse events summaries will be provided by treatment group and by before and after the beginning of the COVID-19 pandemic.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available, abnormalities will be flagged. Descriptive statistics will be provided by treatment and visit/time and will be presented graphically.

Other safety evaluations

Treatment-emergent changes in ocular and systemic parameters will be summarized descriptively by treatment and visit.

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12.7 Interim analyses

There will be one interim analysis after the last patient completes his/her Week 52 (primary analysis time point) visit.

The presentation of tables, listings, and figures will include data up to patients' date of Week 52 visit (inclusive). For adverse events and concomitant medications, Week 52 data including 30 days after patients' last IP administration at Week 48 will be included. All available data for patients discontinuing the study prior to Week 52 will be included in the interim analysis.

This interim analysis will be the primary analysis. There will be no hypothesis testing at Week 104. Therefore, no adjustment of the statistical significant level will be made to tests performed at Week 52.

12.8 Sample size calculation

12.8.1 Primary endpoint

The primary efficacy variable is change in BCVA from Baseline. The primary analysis time point is Week 52.

As suggested by the US regulatory authority, a non-inferiority margin of 4 letters is considered a clinically acceptable difference of brolucizumab 6 mg dosed every 4 weeks compared to aflibercept 2 mg dosed every 4 weeks in a previously treated population and will be utilized in this study.

In SAVE study (Brown 2013) of ranibizumab (n=87), a standard deviation of 6.4 letters for the change in BCVA from Baseline was observed at Month 3. In ASSESS study (Singh 2015) (n=26), a standard deviation of 9.2 letters was obtained at Month 12. In this study, a standard deviation of 10 letters for the change in BCVA from Baseline to Week 52 in pre-treated patients is assumed.

To meet US regulatory authority recommendation for safety assessment, data for brolucizumab 6 mg dosed every 4 weeks from at least 300 subjects with 12-month exposure are required. Thus, 450 subjects will be needed with a 2:1 ratio to brolucizumab 6 mg q4 weeks (300 subjects) and aflibercept 2 mg q4 weeks (150 subjects). This sample size is sufficient to demonstrate non-inferiority (margin = 4 letters) of brolucizumab 6 mg q4 weeks versus aflibercept 2 mg q4weeks with respect to BCVA change from Baseline to Week 52 at a two-sided alpha level of 0.05 with a power of approximately 97% assuming equal efficacy and a common standard deviation of 10 letters. To account for an assumed dropout rate of 12% before Week 52 visit, a total of 513 subjects (342 subjects to the brolucizumab 6 mg q4w arm and 171 to the aflibercept 2 mg q4w arm) will be randomized. The nQuery Advisor 7.0 was used for the above sample size calculations.

[redacted]

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 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 (e.g., 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 (SOPs) 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

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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.

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]

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Table 16-1 Clinically notable laboratory values

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

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16.2 Appendix 2: Liver event and laboratory trigger definitions and follow-up requirements

Table 16-2 Liver event and laboratory trigger definitions

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

* These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

[redacted]

16.3 Appendix 3: Specific renal alert criteria and actions and event follow-up

Table 16-3 Specific renal alert criteria and actions

Serum Event	
Serum creatinine increase 25 – 49% compared to Screen Visit	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to Screen Visit	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR)≥150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at Investigator's discretion) until either: Event resolution: sCr within 10% of Screen Visit or protein-creatinine ratio within 50% of Screen Visit, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	