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RTH258

Clinical Trial Protocol CRTH258B2304 / NCT04058067

A One-Year, Randomized, Double-Masked, Multicenter, Phase III, Two-Arm Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Chinese Patients with Visual Impairment Due to Diabetic Macular Edema (KINGLET)

Document type:	Amended Clinical Trial Protocol
EUDRACT number:	Not applicable
Version number:	02 (Clean)
Clinical Trial Phase:	III
Release date:	08-Oct-2021

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

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List of abbreviations

ACR	albumin-creatinine ratio
ADA	anti-drug antibody
AE	adverse event
AMD	age-related macular degeneration
ANOVA	analysis of variance
ARs	analysis restrictions
BCVA	best-corrected visual acuity
BL	Baseline
CFR	Code of Federal Regulation
CMO & PS	Chief Medical Office and Patient Safety
CNV	Choroidal neovascularization
COA	Clinical Outcome Assessment
COVID-19	Coronavirus disease 2019
CRA	Clinical research associate
CRC	Central Reading Center
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSFT	central subfield thickness
[redacted]	[redacted]
CSR	clinical study report
CTT	Clinical Trial Team
DAA	Disease Activity Assessment
DAR	dose administration record
DDE	Direct Data Entry
DM	Diabetes mellitus
DMC	Data Monitoring Committee
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Scale
EC	Ethics committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
ESI	event of special interest
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiography
FAS	Full analysis set
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply

[redacted]

HbA1c	Hemoglobin A1c
hCG	Human chorionic gonadotropin
HCP	Health care professionals
HRQL	Health-Related Quality of Life
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human
IEC	Independent Ethics Committee
ILM	inner limiting membrane
IN	Investigator notification
IOI	Intraocular inflammation
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional Review Board
IRF	Intraretinal fluid
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
IVT	Intravitreal
kDa	Kilodaltons
LFT	Liver function test
LLOQ	lower limit of quantification
LOCF	Last observation carried forward
MAR	missing at random
MD	Medical Doctor
ME	Macular edema
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMRM	Mixed model for repeated measures
MoA	Mode of Action
nAMD	Neovascular age-related macular degeneration
NEI	National Eye Institute
NIH	National Institutes of Health
NIM	Non-inferiority margin
OCT	Optical coherence tomography
PCR	protein-creatinine ratio
PD	Protocol Deviation
PDR	Proliferative diabetic retinopathy
PK	pharmacokinetic(s)
PPS	Per Protocol Set/Protocol analysis set
PT	Preferred Term
q12w	every 12 weeks
q4w	every 4 weeks
q6w	every 6 weeks

[redacted]

q8w	every 8 weeks
QMS	Quality Management System
QoL	Quality of Life
RAO	Retinal Artery Occlusion
RO	Retinal vascular occlusion
RV	Retinal vasculitis
RPE	Retinal Pigment Epithelium
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
scFv	single-chain fragment variable
SD-OCT	Spectral domain optical coherence tomography
SOC	System Organ Class
SOP	Standard Operation Procedure
SRF	Subretinal fluid
SUN	standardization uveitis nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reactions
USM	Urgent Safety Measures
US	United States
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VFQ-25	Visual Functioning Questionnaire-25
WHO	World Health Organization
WoC	Withdrawal of Consent
YAG laser	Yttrium aluminum garnet laser

[redacted]

Glossary of terms

Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug 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.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
eSource DDE	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Masked/evaluating investigator	For the entire study duration and all study patients, 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 active/sham injections)
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Patient	An individual with the condition of interest
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.

[redacted]

Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Unmasked/treating investigator	For the entire study duration and all study patients, the treating investigator only performs the treatment (injection active/sham) and assesses patient safety following the active/sham injections
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Visual acuity assessor	For the entire study duration and all study patients, the visual acuity assessor (which could be a masked/evaluating investigator) performs the BCVA assessment and is masked to the assigned treatment
Withdrawal of study consent (WoC)/ Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

[redacted]

Amendment 2 08-Oct-2021

Amendment rationale

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

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

This amendment also includes the changes back to the original protocol in Section 5.2 and Section 6.2.2 based on the National Medical Products Administration (NMPA)'s comment during the protocol amendment v01 (dated on 10Jun2020) review.

Some other administrative changes have also been incorporated.

Changes to the protocol

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

- Section 1.1 Background: Information added to describe Urgent Safety Measures
- Section 4.5 Risk and benefits: Information added to describe Urgent Safety Measures and additional information on gender imbalance on IOI following brolucizumab treatment
- Section 6.7.2 Instruction for administering study treatment: Requirement of treatment discontinuation was added if subject developed RV and/or RO, in both arms.
- Section 8.4.3 Ophthalmic examination: Requirement of treatment discontinuation was added if subject developed RV and/or RO.
- Section 9.1.1 Discontinuation of study treatment: Requirement of treatment discontinuation was added if subject developed RV and/or RO.
- Section 9.1.2 Clarified the definition of Withdrawal of Consent (WoC).

Other changes incorporated in this amendment

- Glossary of teams has been updated to the latest template wording
- Section 6.2.1.1 Permitted concomitant therapy requiring caution and/or action: added recommendations on the time window for a study subject to receive the COVID-19 vaccine
- Section 5.2 and Section 6.2.2: Changes related to the COVID-19 pandemic in Amendment 1 were reverted back to the original protocol v00 based on the NMPA's comment on Amendment 1.

[redacted]

- Section 8.5.2 To make consistent with the following wordings (approximately 24 consented subjects to obtain approximately 12 subjects per treatment arm to maintain masking).
- Other minor clarifications and corrections were made where applicable.

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

IRBs/IECs

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

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

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

[redacted]

Amendment 1 10-Sep-2020

Amendment rationale

The main purpose of this amendment is to provide clarification and guidance on safety assessments in accordance to the urgent safety measure regarding the post-marketing reports with brolucizumab (Beovu®) in the treatment of neovascular age-related macular degeneration (nAMD), which were identified as retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation that may result in severe vision loss. In addition, the amendment includes the modifications due to Coronavirus disease 2019 (COVID-19) pandemic.

Changes to the protocol

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

- Section 1.1 Background: Information was added to describe new safety signal from post-marketing case reports.
- Section 6.2.2 Prohibited medication: Restrictions in use of corticosteroids have been removed to provide flexibility using systemic steroids for the treatment of AEs during the study period at the investigator's discretion.
- Section 6.7.2 Instructions for prescribing and taking study treatment: Additional guidance was added to this section emphasizing that if any sign of intraocular inflammation (IOI) is present, an IVT injection **must not** be performed and patients should be treated for IOI according to clinical practice.
- Additional examination and assessments included to fully characterize cases of IOI were made in the following sections:
  - Table 8-1 Assessment schedule
  - Section 8.3.3 Color fundus photography and fluorescein angiography
  - Section 8.4.3 Other safety evaluations: slit lamp and indirect fundus examination
  - Section 8.4.4 Appropriateness of safety measurements

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

- Section 5.2 Exclusion criteria 20
- Section 6.2.2 Prohibited medication Table 6-2
- Section 7 Informed consent procedures
- Section 8 Visit Schedule and Assessments
- Section 8.4 Safety
- Section 8.4.1 Laboratory evaluations
- Section 12 Data analysis and statistical methods

[redacted]

Other changes were incorporated in the following sections:

- Table 2-1 Objectives and related endpoints: aligned with Section 12.5.1.2.
- Section 6.4 Treatment masking: Language was added to clarify unmasked investigator/site personnel must not be switched to a masked role at any time after randomization.
- Table 8-1 Assessment schedule: The assessment schedule of Visual Function Questionnaire-25 was updated from Visit 9 to Visit 10 due to the typographical error in previous version.
- Section 8.2 Subject demographics/other baseline characteristics: Removed ethnicity since it was not collected in the study.
- Section 8.4.3 Other safety evaluations: Clarification of Post-injection IOP measurement timing.
- Section 8.5.3 Other assessments
- Section 10.1.3 SAE reporting: Clarification of the SAE reporting period.
- Section 12 Data analysis and statistical methods: Language was updated to clarify primary and supplementary estimands and analyses based on estimands.
- [redacted]
- Section 15 References
- List of Abbreviations

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

IRBs/IECs

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

This amendment is primarily required for patient safety (i.e. necessary to eliminate immediate hazards to the trial subjects per ICH GCP 3.3.8). Therefore, the changes related to the emerging safety issue will be implemented prior to IRB/IEC and Health Authority approval, however the remaining changes will not be implemented until after receipt of IRB/IEC and Health Authority approval according to local regulations.

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

[redacted]

Protocol summary

Protocol number	RTH258B2304
Full Title	A One-Year, Randomized, Double-Masked, Multicenter, Phase III, Two-Arm Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Chinese Patients with Visual Impairment Due to Diabetic Macular Edema (KINGLET)
Brief title	Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Chinese Patients with Visual Impairment Due to Diabetic Macular Edema
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate the efficacy and safety of brolucizumab in treatment of Chinese patients with visual impairment due to Diabetic Macular Edema (DME).
Primary Objective(s)	The primary objective of this study is to demonstrate that brolucizumab is non-inferior to aflibercept with respect to the visual outcome after up to one year of treatment
Secondary Objectives	1. To estimate the proportion of patients treated at every 12 weeks (q12w) frequency with brolucizumab 2. To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab 3. To evaluate the functional and anatomical outcome with brolucizumab relative to aflibercept 4. To evaluate the effect of brolucizumab relative to aflibercept on the Diabetic Retinopathy (DR) status 5. To assess the safety of brolucizumab relative to aflibercept 6. To evaluate the effect of brolucizumab relative to aflibercept on patient-reported outcomes (Visual Functioning Questionnaire-25 (VFQ-25)) 7. To confirm the systemic brolucizumab exposure in a subset of patients 8. To assess the immunogenicity of brolucizumab over one year of treatment
[redacted]	
Study design	The study is a randomized, double-masked, multi-center, active-controlled, 2 armed study in Chinese patients with DME. Patients who meet all the inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio to one of two treatment arms: • Brolucizumab 6 mg: 5 x every 6 weeks (q6w) loading then q12w or every 8 weeks (q8w) maintenance • Aflibercept 2 mg: 5 x every 4 weeks (q4w) loading then q8w maintenance
Population	The study population will be male and female Chinese patients ≥ 18 years old with visual impairment due to DME. Approximately 335 Chinese patients will be screened (20% screening failure rate expected) and approximately 268 (134 per arm) patients will be randomized in approximately 25 centers.
Key Inclusion criteria	1. Signed informed consent must be obtained prior to participation in the study. 2. Patients ≥18 years of age at screening 3. Patients with type 1 or type 2 diabetes mellitus (DM) and Hemoglobin A1c (HbA1c) of ≤10% at screening 4. Medication for the management of diabetes must have been stable within 3 months prior to randomization and is expected to remain as stable as medically acceptable during the course of the study
[redacted]	

	5. Study Eye Visual impairment due to DME with: • Best-corrected visual acuity (BCVA) score between 78 and 23 letters, inclusive, using ETDRS visual acuity (VA) testing charts at a starting testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/320) at screening and baseline • DME involving the center of the macula, with central subfield retinal thickness (e.g. measured from retinal pigment epithelium (RPE) to the inner limiting membrane (ILM) inclusively) of ≥320 µm on Spectral domain optical coherence tomography (SD-OCT) at screening. Eligibility is determined by Investigator's assessment at time of Screening. If both eyes are eligible, the eye with the worse visual acuity will be selected for study eye. However, the investigator may select the eye with better visual acuity, based on medical reasons or local ethical requirements.
Key Exclusion criteria	• Active Proliferative diabetic retinopathy (PDR) in the study eye as per investigator • Concomitant conditions or ocular disorders in the study eye at screening or baseline which could, in the opinion of the investigator, prevent response to study treatment or may confound interpretation of study results, compromise visual acuity or require medical or surgical intervention for the duration of the study (e.g. cataract, vitreous hemorrhage, retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization (CNV) of any cause) • Any active intraocular or periocular infection or active intraocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis, uveitis) in study eye at screening or baseline • Structural damage of the fovea in the study eye at screening likely to preclude improvement in visual acuity following the resolution of macular edema (ME), including atrophy of the retinal pigment epithelium, subretinal fibrosis, laser scar(s), epiretinal membrane involving fovea or organized hard exudate plaques • Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication or according to investigator's judgment at Screening or Baseline • Neovascularization of the iris in the study eye at screening or baseline • Evidence of vitreomacular traction in the study eye at screening or baseline which in the opinion of the investigator, affects visual acuity • Previous treatment with any anti-vascular endothelial growth factor (VEGF) drug or investigational drugs in the study eye
Study treatment	Brolucizumab 6 mg/0.05mL Aflibercept 2 mg/0.05mL
Efficacy assessments	• BCVA with ETDRS-like chart at 4 meters • Anatomical markers on SD-OCT • ETDRS Diabetic Retinopathy Severity Scale (DRSS) score based on 7-field stereo Color Fundus Photography • Vascular leakage evaluation by fluorescein angiography (FA)
Pharmacokinetic assessments	Systemic brolucizumab exposure assessment will be performed on approximately 24 consented patients or approximately 12 patients per treatment arm to maintain masking.
Key safety assessments	• Adverse events (AEs), including AEs of special interest • Physical examination, vital signs • Standard ophthalmic examination (Biomicroscopy (slit lamp examination), Intraocular pressure, Indirect ophthalmoscopy) • Hematology/clinical chemistry/urinalysis
Other assessments	• Patient Reported Outcome: National Eye Institute (NEI) VFQ-25 • Pharmacokinetics (PK) of brolucizumab

[redacted]

	• Anti-Drug Antibodies (ADA) of brolucizumab
Data analysis	**Primary analysis data set:** The primary data set for efficacy evaluation is the full analysis set (FAS) with missing values imputed by last observation carried forward (LOCF). The FAS includes all randomized patients who receive at least one intravitreal (IVT) injection. Sensitivity and supportive analyses will be performed using the per protocol analysis set (PPS) and alternative methods of handling missing values. **Primary and key secondary endpoints:** The primary endpoint is the change from baseline in BCVA at Week 52. The key secondary efficacy endpoint involved in confirmatory testing is average change from baseline in BCVA averaged over the period Week 40 to Week 52. Additional key secondary endpoints are proportion of patients maintained at q12w up to Week 52 and proportion of patients maintained at q12w up to Week 52 within those patients that qualified for q12w at Week 36 (for brolucizumab treatment arm only) **Statistical Hypotheses and testing strategy:** The following non-inferiority hypotheses are related to a non-inferiority margin (NIM) of 4 letters: B = Brolucizumab 6 mg - 5 x q6w loading then q12w/q8w maintenance A = Aflibercept 2 mg - 5 x q4w loading then q8w maintenance **H01**: μB – μA ≤ -4 letters vs. **HA1**: μB – μA > -4 letters **H02:** φB – φA ≤ -4 letters vs. **HA2**: φB – φA > -4 letters Where μB and μA are the corresponding unknown true mean changes from baseline in BCVA at Week 52; φB and φA are the corresponding unknown true mean changes from baseline in BCVA averaged over the period Week 40 to Week 52; These 2 hypotheses will be tested sequentially in the order of their numbering (HAn, n=1, 2). Consequently, confirmatory testing of the second hypothesis requires rejection of the first null hypothesis. In this setting, each hypothesis will be assessed at a one-sided significance level of 0.025, while keeping the global type I error rate at 0.025. **Primary statistical method:** Analysis of variance (ANOVA) models will be used to test the treatment differences regarding the endpoints 'change from baseline in BCVA at Week 52' and 'change from baseline in BCVA averaged over the period Week 40 to Week 52'. The models will include baseline BCVA category (≤65, >65 letters) and age category (<65, ≥65 years) as factors. Two-sided 95% confidence intervals (CI) for the least square means difference (brolucizumab - aflibercept) will be presented. Within the specified testing procedure, non-inferiority will be established if the lower limit of the corresponding 95% CI is greater than -4 letters. **Sample size justification:** A sample size of 120 patients per arm will allow to demonstrate a non-inferiority (NIM of 4 ETDRS letters) of brolucizumab 6 mg vs. aflibercept 2 mg with respect to the BCVA change from baseline at Week 52, with 80% power at a one-sided alpha level of 0.025, assuming equal means and a common standard deviation of 11 letters. Assuming that averaging over the 4 time points will not lead to an increase in the standard deviation a power of at least 80% can also be expected for its corresponding non-inferiority claim. To account for a drop-out rate of 10%, a total of 268 (134 per arm) patients will need to be randomized.
Key words	Diabetic Macular Edema, intravitreal injection, brolucizumab, aflibercept, double-masked

[redacted]

1 Introduction

1.1 Background

Diabetes mellitus (DM) is the most common endocrine disease in developed countries, with prevalence estimates ranging between 2 to 5% of the world population. Diabetic retinopathy (DR) and diabetic macular edema (DME) are common microvascular complications in patients with diabetes and may have a debilitating impact on visual acuity (VA), eventually leading to blindness. DME is a frequent manifestation of DR (Lee et al 2015) and is the major cause of visual loss in patients with DR.

For anti-vascular endothelial growth factor (VEGF) agents like ranibizumab or aflibercept, a favorable benefit risk ratio was demonstrated with superior efficacy versus the previous standard of care (laser photocoagulation) in large Phase 3 programs that consequently led to their approval for the treatment of DME (Ziemssen et al 2017; Korobelnik et al 2014). Anti-VEGF treatment led to clinically relevant improvements of BCVA, reduction of fluid accumulation and decreased severity of diabetic retinopathy.

Current available therapies

The current treatment options for patients with DME are: laser photocoagulation, intravitreal (IVT) corticosteroids, IVT corticosteroid implants, or IVT anti-VEGF. Due to the efficacy and safety profile of anti-VEGF therapy, it has become the first-line treatment. Corticosteroids are used as a second line treatment and focal/grid laser photocoagulation remains a therapeutic option, but with a lower expected benefit compared with steroid and anti-VEGF therapy.

Currently available anti-VEGF treatments require frequent regular IVT injections which can be burdensome to patients and health care professionals (HCP). Thus, despite the treatment success of existing anti-VEGFs, there remains a need for further treatment alternatives to improve response rate and/or reduce treatment burden and injection frequency in patients with DME (Mitchell et al 2011; Smiddy 2011; Lang et al 2013; Virgili et al 2014; Agarwal et al 2015).

Brolucizumab

Brolucizumab, formerly known as RTH258 and ESBA1008, is a humanized single-chain fragment variable (scFv), binding to VEGF-A (i.e. interfering with activation of VEGF-R1 and R2 on endothelial cells) with a molecular weight of ~26 Kilodaltons (kDa) that has also being developed for the treatment of choroidal neovascularization (CNV) associated with neovascular age-related macular degeneration (nAMD).

The characteristics of brolucizumab allow delivery of a high molar dose via intravitreal injection. Higher molar doses are expected to lead to longer presence of relevant drug levels in the retina. In addition, a low molecular weight and high concentration gradient between the vitreous and the retina may increase drug distribution to the target site of action, supporting effective control of anatomical disease activity. This could potentially translate into a more durable efficacy and a reduced treatment burden (number of injections) for the patient and HCP.

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Brolucizumab in nAMD

In a single ascending dose Phase I study (C-10-083), the median time until age-related macular degeneration (AMD) patients fulfilled protocol defined criteria for receipt of standard of care treatment was 30 days longer for brolucizumab 3 mg (p=0.037) and 6 mg (p=0.036) versus ranibizumab. In a separate repeat dosing study (C-12-006) comparing brolucizumab 6 mg (every 8 weeks (q8w), then every 12 weeks (q12w) administration) against aflibercept (q8w administration), brolucizumab achieved comparable visual outcome during the loading and q8w phase, with a lower number of patients requiring additional rescue treatments (5 vs. 10, respectively). Brolucizumab demonstrated a trend for greater improvements and more stability in retinal anatomy during the 4 cycles of q8w dosing (up to Week 40), e.g. simultaneous resolution of intraretinal and subretinal fluid (SRF) which was achieved in 61% of brolucizumab patients versus 35% of aflibercept patients at Week 40. In the Phase III studies RTH258-C001 (HAWK) and RTH258-C002 (HARRIER), brolucizumab demonstrated non-inferiority to aflibercept in mean change in best-corrected visual acuity (BCVA) from baseline to Week 48 in both trials. These results were achieved while a majority of patients on brolucizumab 6 mg – 56% in HAWK and 51% in HARRIER – were maintained on a q12w dosing interval following the loading phase through Week 48. Significantly fewer patients on brolucizumab had disease activity at Week 16 (head-to-head comparison based on a matching dosing regimen) with a relative decrease of 30% (P = 0.0022) versus aflibercept. Significantly fewer patients on brolucizumab had intraretinal fluid (IRF) and/or subretinal fluid (SRF), with a 35% and 33% reduction relative to aflibercept at Week 16 (P < 0.001 for both) in HAWK and HARRIER, respectively, and a 31% and 41% reduction relative to aflibercept at Week 48 in HAWK and HARRIER, respectively (P < 0.0001 for both). Brolucizumab 6mg achieved superior reductions in central subfield thickness (CSFT) versus aflibercept in both the head-to-head and maintenance phases (P = 0.0016 and P = 0.0023 at Week 16 and Week 48, respectively, in HAWK; P < 0.0001 at both Week 16 and Week 48 in HARRIER). Brolucizumab safety was comparable to aflibercept, with the overall incidence of adverse events (AEs) balanced across all treatment groups in both studies.

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

Summary

Ranibizumab, aflibercept and brolucizumab all inhibit the activity of VEGF-A and both ranibizumab and aflibercept have demonstrated efficacy in the treatment of patients with nAMD. Both ranibizumab and aflibercept have also consistently demonstrated efficacy in the treatment of patients with visual impairment due to DME. These findings support the evaluation of

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brolucizumab in DME patients. Furthermore, the efficacy profile of brolucizumab in nAMD patients indicates a potential of brolucizumab to differentiate versus existing anti-VEGFs on duration of action and anatomical efficacy in DME patients:

- The longer duration of action is supported by the following outcomes of the phase I and II nAMD studies with brolucizumab 6 mg dose:
  - Maximum improvements in BCVA and CSFT at Week 4 for ranibizumab versus Week 6 for brolucizumab
- Greater CSFT stability during q8w maintenance versus aflibercept:
  - Fewer rescue treatments versus aflibercept in q8w phase
- The aforementioned results were confirmed by the nAMD 48-week study results (HAWK and HARRIER studies), which demonstrated:
  - Visual gains at Week 48 achieved with 56% (HAWK) and 51% (HARRIER) of patients treated following a q12w regimen
  - Superior reduction in CSFT versus aflibercept
  - The potential for less frequent injections of brolucizumab as compared to aflibercept
  - Lower proportion of patients with intra- and/or subretinal fluid

These considerations support the initiation of a Phase III program to evaluate the efficacy and safety of brolucizumab in treatment of patients with visual impairment due to DME with the objective to evaluate the potential to reduce the treatment burden for patients.

1.2 Purpose

The purpose of this study is to evaluate the efficacy and safety of brolucizumab in treatment of Chinese patients with visual impairment due to DME.

2 Objectives and endpoints

For the detailed description of endpoints and their statistical analysis, please refer to Section 12.4 for primary and key secondary endpoints, Section 12.5 for other secondary [redacted] endpoints.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that brolucizumab 6mg is non-inferior to aflibercept 2mg with respect to the visual outcome after up to one year of treatment	• Change from baseline in BCVA at Week 52 • Change from baseline in BCVA averaged over a 3 month period (from Week 40 to Week 52)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To estimate the proportion of patients treated at q12w frequency with brolucizumab	• Proportion of patients maintained at q12w up to Week 52
• To estimate the predictive value of the first q12w cycle for maintenance of q12w treatment with brolucizumab	• Proportion of patients maintained at q12w up to Week 52, within those patients that qualified for q12w at Week 36

[redacted]

Objective(s)	Endpoint(s)
• To evaluate the functional and anatomical outcome with brolucizumab relative to aflibercept	• Change from baseline by visit up to Week 52 in BCVA and in parameters derived from SD-OCT, Color fundus photography and Fluorescein angiography
• To evaluate the effect of brolucizumab relative to aflibercept on the Diabetic Retinopathy status	• Change in ETDRS Diabetic Retinopathy Severity Scale (DRSS) score up to Week 52
• To assess the safety of brolucizumab relative to aflibercept	• Continuous incidence of Ocular and Non-ocular AEs, vital signs and laboratory values up to Week 52
• To evaluate the effect of brolucizumab relative to aflibercept on patient-reported outcomes (VFQ-25)	• Change in patient reported outcomes (VFQ-25) total and subscale scores from baseline up to Week 52
• To confirm the systemic brolucizumab exposure in a subset of patients	• Systemic brolucizumab concentration approximately 24 hours after initial and final loading phase doses in a sub set of patients
• To assess the immunogenicity of brolucizumab over one year of treatment	• Anti-drug antibody status at screening and up to Week 52 in brolucizumab arm
[redacted]	

3 Study design

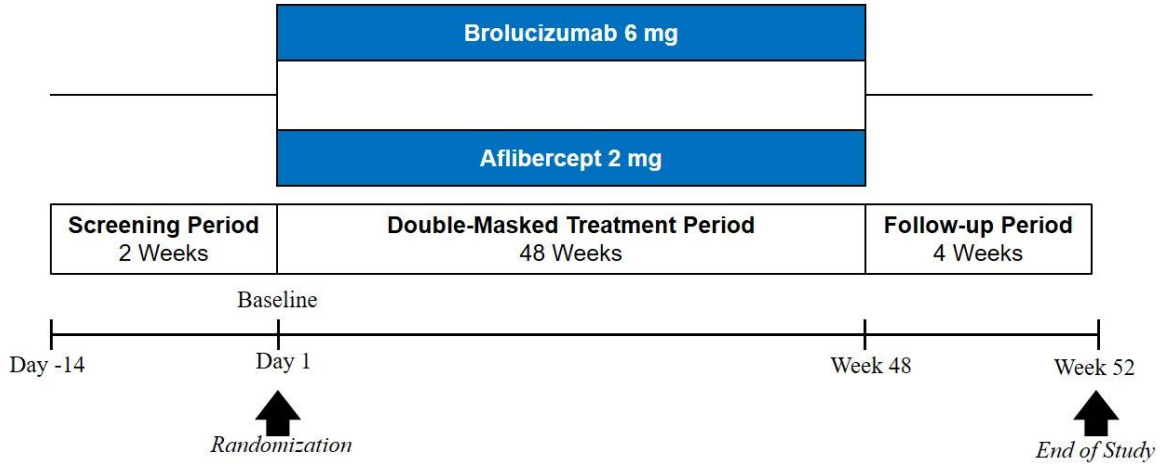
The study is a randomized, double-masked, multi-center, active-controlled, 2 armed study in patients with DME.

Patients who consent will undergo screening assessments to evaluate their eligibility based on the inclusion and exclusion criteria. Patients who meet all the inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio to one of two treatment arms:

- Brolucizumab 6 mg: 5 x q6w loading then q12w or q8w maintenance
- Aflibercept 2 mg: 5 x q4w loading then q8w maintenance

[redacted]

Figure 3-1 Study design



Screening period: Day -14 to Day -1

A screening period of up to 2 weeks will be used to assess eligibility.

One time rescreening of patients is allowed, except for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the patient. As long as testing can be repeated within 14 days of the first screening, the other screening assessments do not need to be repeated. If rescreening is to occur beyond 14 days from the original screening visit date, then all screening procedures must be repeated. Medical judgment should be exercised to ensure that treatment of DME is not withheld in order for a patient to participate in the study.

Double masked treatment period: Day 1 to Week 48

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

Only one eye will be selected as study eye and treated with study medication.

The baseline visit is defined as Day 1/Visit 1, and End of treatment (EOT) visit as Visit 15 (Week 48).

A study visit schedule will be established at the time of randomization for all patients. All efforts should be made to adhere to this study visit schedule ±7day window (except Baseline/Day 1 where no window is allowed). In addition, for a given protocol visit (except Baseline/Day 1), assessments can be performed on two consecutive days in which both days must occur within the ±7 day window. Treatment is intended to be administered on the day of study visit, or if this is not possible, within 3 days after the first day of a study visit when the per-protocol assessments took place. For Baseline/Day 1, treatment must be given on the same day of the visit. Also, two consecutive injections should be spaced by at least 21 days.

Patients must have confirmed type 1 or type 2 diabetes at screening. Adequate glycemic control must be confirmed by an HbA1c level ≤10 % at screening.

Post-treatment follow-up period: Week 48 to Week 52:

For all patients, the last study assessment will be performed at End of Study (EOS) visit (Week 52), four weeks (±7 days) after the last active study treatment in this study.

[redacted]

Patients withdrawn from the study prior to study completion will be asked to return for an early discontinuation visit (EOS visit), four weeks (±7 days) following their last study treatment administration.

4 Rationale

4.1 Rationale for study design

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

- in addition to every 4-week visits for all patients for 1 year, extra visits are scheduled at Weeks 6 and 18 for both treatment arms in order to maintain the double-masking despite the different treatment administration schedule between the two treatment arms
- the patients will receive active or sham injection at each protocol visit except Weeks 20, 28 and 52 (No scheduled treatment for any arm)
- Disease activity assessment (DAA) will be performed for both arms
- to fulfil the double-masking requirement, the investigational site will have masked and unmasked staff

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

4.2 Rationale for dose/regimen and duration of treatment

The doses and regimen for brolucizumab and aflibercept are based on the following considerations:

- Brolucizumab is well tolerated at a dose of 6 mg administered at a q4w regimen during the loading phase, based on the previous clinical phase III program in which 1088 patients with nAMD received brolucizumab. The nAMD study results regarding q12w/q8w maintenance regimen support stretching the minimum interval between injections to 6 weeks to reduce the treatment burden (see Section 1.1 for further details).
- Current evidence from large anti-VEGF pivotal studies in DME combined with the evidence detailed above supports an extended period of intense treatment (loading regimen) is required to achieve maximal BCVA gain. Hence the loading regimen was extended to Week 24 for brolucizumab.
- Route of administration is intravitreal injection as for all anti-VEGF treatments currently approved for the treatment of DME and other retinal diseases related to macular edema. The intraocular level of anti-VEGF treatments such as brolucizumab would not be sufficient following systemic administration to ensure treatment efficacy. Thus, brolucizumab has to be injected intravitreally.
- Aflibercept is applied as per the current approved label in China.

[redacted]

Study duration of 1 year (with treatment of approximately 12 months) is warranted to assess longer-term efficacy and safety and to assess the q12w/q8w options for brolucizumab over time.

4.3 Rationale for choice of comparator

Aflibercept 2 mg q8w is an established standard of care option and has been chosen as comparator for this study due to the consistency of the approved dose and posology of aflibercept (Eylea®) across many countries especially European Union (EU) and United States (US) for the targeted indication as compared to other approved anti-VEGF treatments.

Therefore, using the same study comparator as in global pivotal studies will allow the comparison of the results between China and global study populations.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

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

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements 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.

Ranibizumab and aflibercept (both approved inhibitors of VEGF-A) have consistently demonstrated efficacy in VEGF-driven retinal pathologies, including DME, with benefits outweighing the risks. Assuming a corresponding class-effect, it is justified to expect that brolucizumab (having the same mode of action (MoA) as ranibizumab and aflibercept) will likewise be efficacious and have a similar safety profile in the DME indication. In both Phase III studies (HAWK, HARRIER) in nAMD, brolucizumab demonstrated non-inferiority to aflibercept in mean change in BCVA from baseline to Week 48. These results were achieved while a majority of patients on brolucizumab 6 mg – 56% in HAWK and 51% in HARRIER – were maintained on a q12w dosing interval following the loading phase through Week 48, i.e. with a reduced treatment frequency compared to aflibercept.

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of IOI have been reported following brolucizumab injection. These immune mediated adverse events may occur following the first intravitreal injection. Discontinuation of study treatment is required in subjects who develop these events. In addition, subjects who experience IOI may be at risk of developing retinal vasculitis and/or retinal vascular occlusion and should be closely monitored.

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

[redacted]

Brolucizumab safety was comparable to aflibercept, with the overall incidence of adverse events balanced across all treatment groups in both studies when treatment interval is not less than every 8 weeks after the first 3 monthly initial doses (loading phase). The risk/benefit assessment for brolucizumab remains positive.

The higher intravitreal concentration of brolucizumab (approximately 11-time higher for 6 mg brolucizumab vs 2 mg aflibercept) is expected to confer a longer duration of effect in DME that will translate into a reduced frequency of injections with a non-inferior efficacy. A reduced treatment frequency will provide benefit to patients and caregivers/physicians. Further details of the known and potential risks and benefits associated with brolucizumab are presented in the Investigator's Brochure (IB).

5 Population

The study population will be male and female Chinese patients ≥18 years old with visual impairment due to DME. Approximately 335 Chinese patients will be screened (20% screening failure rate expected) and approximately 268 (134 per arm) patients will be randomized in approximately 25 centers.

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. Patients ≥18 years of age at screening
3. Patients with type 1 or type 2 diabetes mellitus and HbA1c of ≤10% at screening
4. Medication for the management of diabetes must have been stable within 3 months prior to randomization and is expected to remain as stable as medically acceptable during the course of the study
5. Study Eye

   Visual impairment due to DME with:

   - BCVA score between 78 and 23 letters, inclusive, using ETDRS visual acuity testing charts at a starting testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/320) at screening and baseline
   - DME involving the center of the macula, with central subfield retinal thickness (e.g. measured from retinal pigment epithelium (RPE) to the inner limiting membrane (ILM) inclusively) of ≥320 μm on SD-OCT at screening. Eligibility is determined by Investigator's assessment at time of Screening.

   If both eyes are eligible, the eye with the worse visual acuity will be selected for study eye. However, the investigator may select the eye with better visual acuity, based on medical reasons or local ethical requirements.

5.2 Exclusion criteria

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

Ocular concomitant condition/disease

1. Active Proliferative Diabetic Retinopathy in the study eye as per investigator

[redacted]

2. Concomitant conditions or ocular disorders in the study eye at screening or baseline which could, in the opinion of the investigator, prevent response to study treatment or may confound interpretation of study results, compromise visual acuity or require medical or surgical intervention for the duration of the study (e.g. cataract, vitreous hemorrhage, retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization of any cause)
3. Any active intraocular or periocular infection or active intraocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis, uveitis) in study eye at screening or baseline
4. Structural damage of the fovea in the study eye at screening likely to preclude improvement in visual acuity following the resolution of macular edema, including atrophy of the retinal pigment epithelium, subretinal fibrosis, laser scar(s), epiretinal membrane involving fovea or organized hard exudate plaques
5. Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication or according to investigator's judgment at Screening or Baseline
6. Neovascularization of the iris in the study eye at screening or baseline
7. Evidence of vitreomacular traction in the study eye at screening or baseline which in the opinion of the investigator, affects visual acuity
8. Presence of amblyopia, amaurosis or ocular disorders with vision <20/200 (35 letters) in the fellow eye at screening or baseline
9. History of idiopathic or autoimmune uveitis in the study eye

Ocular treatments

10. Previous treatment with any anti-VEGF drug or investigational drugs in the study eye
11. Use of dexamethasone intravitreal implant (Ozurdex) or fluocinolone acetonide intravitreal implant (Iluvien) in study eye at any time. Prior use of other intraocular or periocular corticosteroids in the study eye is not an exclusion provided at least 6-month wash-out prior to baseline
12. Laser photocoagulation (focal/grid or panretinal) in the study eye during the 3-month period prior to baseline
13. Intraocular surgery including Yttrium aluminum garnet laser (YAG laser) in the study eye during the 3-month period prior to baseline
14. History of vitreoretinal surgery in study eye
15. Aphakia with the absence of posterior capsule in the study eye

Systemic conditions or treatments

16. Stroke or myocardial infarction during the 6-month period prior to baseline
17. Renal failure requiring dialysis or renal transplant
18. Uncontrolled blood pressure defined as a systolic value ≥160 mmHg or diastolic value ≥100 mmHg at screening or baseline
19. Systemic anti-VEGF therapy during the 3-month period prior to baseline
20. Systemic medications known to be toxic to the lens, retina or optic nerve (e.g. deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines and ethambutol) used during the 6-month period prior to baseline

[redacted]

21. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes, or clinically relevant sensitivity to fluorescein dye as assessed by the investigator
22. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
23. History of a medical condition (disease, metabolic dysfunction with exception of type 1 or 2 diabetes mellitus, physical examination finding, or clinical laboratory finding) that, in the judgment of the investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product (IP)
24. Use of systemic investigational drugs within 5 half-lives of baseline, [or within 30 days/until the expected pharmacodynamic effect has returned to baseline], whichever is longer (observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary)

Other

25. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) pregnancy test
26. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the study drug administration and for 3 months after study drug discontinuation. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before baseline. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to baseline). For female patients in the study, the vasectomized male partner should be the sole partner for that patient
    - 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 child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

[redacted]

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 drug

Investigational Drug	**Pharmaceutical Dosage Form**	**Route of Administration**	**Supply type**	**Sponsor (global or local)**
Brolucizumab 6 mg	Solution for injection	Intravitreal use	Open label supply in Sterile glass vial. Blinding at the clinical site by unblinded site personnel	Global
Control Drug	**Pharmaceutical Dosage Form**	**Route of Administration**	**Supply type**	**Sponsor (global or local)**
Aflibercept 2 mg	Solution for injection	Intravitreal use	Open label supply in Sterile glass vial. Blinding at the clinical site by unblinded site personnel	Global

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 consist of a carton that contains 1 single use, sterile glass vial containing brolucizumab 6 mg/0.05 mL.

Aflibercept study kit will consist of a carton that contains 1 single use, sterile glass vial containing aflibercept 2 mg/0.05mL.

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

Novartis will ensure 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/group

At visit 1, subjects will be assigned to one of the following 2 treatment arms in a 1:1 ratio:

- Brolucizumab 6 mg: 5 x q6w loading then q12w/q8w maintenance
- Aflibercept 2 mg: 5 x q4w loading then q8w maintenance

[redacted]

6.1.4 Treatment duration

The planned duration of treatment is 12 months (48 weeks). Discontinuation of study treatment for a subject occurs when study drug will be stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

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 he/she takes after signing the study informed consent. All medications, procedures and significant non-drug therapies (e.g. blood transfusions) administered after the patient was enrolled into the study must be recorded in the appropriate electronic Case Report Form (eCRF) page.

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

6.2.1.1 Permitted concomitant therapy

During the study, if the fellow eye develops visual impairment due to DME or other diseases, it may be treated with standard of care at the discretion of the investigator (i.e. treatment of the fellow eyes with anti-VEGF medication other than brolucizumab is allowed). Treatment of the fellow eye should be scheduled in a way not to disturb the schedule for visits and treatments in the study eyes. Fellow eye treatment will be captured in the eCRF. The fellow eye must be monitored according to routine practice and AEs captured in the eCRF.

In case of development of neovascularization in the study eye during the study, scatter laser therapy or panretinal photocoagulation is permitted at any time during the course of the study as deemed necessary by the masked investigator. The patient can continue to participate in the study and receive study treatment as planned. When laser treatment is performed at the active study treatment visit, it should be performed prior to study medication injection.

Topical ocular corticosteroids administered in the study eye are allowed during the study. Corticosteroids administered via intra-nasal, inhaled or intra-articular route are also permitted during the study.

If cataract surgery is necessary, attempt to schedule cataract surgery $\geq$ 7 days after the most recent study treatment. Study treatment may be resumed $\geq$ 14 days after cataract surgery, assuming an absence of surgical-related complications.

If the subject is planning to receive a COVID-19 vaccine that is authorized by local regulation, it is recommended to receive the vaccine at least 7 days before or after the study treatment visit including Baseline (Day 1) visit.

6.2.2 Prohibited medication

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

[redacted]

Table 6-2 Prohibited medications/procedures

Medications/Procedures	Prohibition period	Action taken
Study eye		
Intra- or periocular corticosteroids (except if needed as short term treatment of AE)	Any time	Discontinue study treatment (except if for treatment of AE)
Anti-VEGF therapy other than assigned study medication	Any time	Discontinue study treatment
Laser photocoagulation (focal/grid)	Before or at Week 32	Continuation of study treatment at the investigators discretion
Any investigational drug, biologic or device	Any time	Discontinue study treatment
Vitrectomy and vitreo-retinal surgery	Any time	Discontinue study treatment
Systemic		
Anti-VEGF therapy	Any time	Discontinue study treatment
Any investigational drug, biologic or device	Any time	Discontinue study treatment
Medications toxic to the lens, retina or optic nerve	Any time	Discontinue study treatment

Standard of care or other treatments according to the investigators practice for DME and other diseases in the fellow eye are permissible at any time and must be recorded in the appropriate eCRF page.

Oral, intravenous, intramuscular, or extensive dermal (> 20% total body surface area) corticosteroids should not be administered within 5 days prior to study drug administration.

6.2.3 Rescue medication

The study eye, in both treatment groups, identified as needing q8w at a previous visit could receive rescue treatments with laser photocoagulation (focal/grid) from week 36 onwards if macular edema (ME) worsening results in a ≥10-letter loss at 2 consecutive visits or ≥15-letter at 1 visit best previous measurement, with BCVA not better than baseline. When applicable, patients could receive both laser photocoagulation and active study treatment as scheduled at the same visit. Patients can continue with the study treatment.

Panretinal photocoagulation is permitted during the study as deemed necessary by the investigator, and the subject can continue the study.

In case the investigator deems it in the best interest of the subject to receive treatment in the study eye, aside from laser, which is prohibited by this protocol, instructions provided in Table 6-2 should be followed.

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 Subject No. consists of the Center Number (4 digit number for Center No. as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it (3 digit number for Subject No.), 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.

Subjects who have been screen failures but are rescreened (see Section 8.1) will be assigned a new Subject No.

6.3.2 Treatment assignment, randomization

At baseline visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms, in a ratio of 1:1. Stratification for systemic exposure sampling will be considered.

The unmasked investigator or her/his delegate will contact the IRT, after receiving confirmation from the masked investigator that the subject fulfills all the inclusion and none of the exclusion criteria. The IRT will assign a randomization number to the subject, which will link the subject to a treatment arm.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A 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. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers.

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

6.4 Treatment masking

Table 6-3 Masking levels

Time or Event			
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single subject unmasked)**
Patients	M	M	M
Site staff[1]	M	M	M
Unmasked site staff (see text for details)	M	U	U
Global Clinical Supply and Randomization Office	U	U	U
Unmasked sponsor staff (see text for details)	M	U	U
Statistician/statistical programmer/ data analysts	M	M	M
Independent committees used for assessing interim results	U	U	U
All other sponsor staff not identified above	M	M	M

[redacted]

Time or Event			
Role	**Randomization list generated**	**Treatment allocation & dosing**	**Safety event (single subject unmasked)**
M: Remains masked U: Can be unmasked [1] In the event of a medical emergency or an AE during the study where the knowledge of subject treatment is required (e.g. in case of suspected unexpected serious adverse reactions (SUSAR)), an individual investigator will have the ability to unmask the treatment assignment for a specific subject.			

The intent of masking is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. Bias could arise from the influence that the knowledge of a specific treatment assignment may have on the recruitment and allocation of subjects, their subsequent care, the assessment of endpoints, the handling of withdrawals, and so on. The essential aim of masking, therefore, is to prevent identification of the treatments by the investigator, subject, and others associated with the conduct of the study until all such opportunities for bias have passed.

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

Unmasking of investigators and personnel directly involved in the conduct of the study will only occur in the case of patient emergencies (see Section 6.6.2), and then at the time of the final analysis (see Section 12), at the conclusion of the study.

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

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

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

[redacted]

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

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

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

6.5 Dose escalation and dose modification

6.5.1 Dose modifications

Deviations to mandatory dose interruptions during the loading phase and/or dose modifications during the whole study are not allowed.

Interruption of study treatment is allowed if warranted by an AE.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Every time the study treatment is to be administered, IRT needs to be accessed by unmasked study personnel for the medication (kit) number. The date and time of all study treatment injections administered during the study and any deviations from the protocol treatment schedule will be captured by the unmasked study personnel or by unmasked field monitor on the appropriate study treatment dispensing form.

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 unmasked study personnel.

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

[redacted]

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
- 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 un-masking can be performed at any time.

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

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

For brolucizumab, the study medication has a 2-part label (base plus tear-off label). A unique medication number is printed on each part of this label, which corresponds to one of the treatment arms. Unmasked study personnel will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the medication kit to the subject, unmasked site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment

Study treatment must be received by a designated unmasked person at the study site, handled and stored safely and properly and kept in a secured location to which only the unmasked investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

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

The unmasked study personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by unmasked monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

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

[redacted]

6.7.2 Instruction for prescribing and taking study treatment

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

There will be two treatment phases for IVT injections with different timing for brolucizumab and aflibercept treatment arms:

Loading Phase

Brolucizumab: In the loading phase, treatment with brolucizumab will occur every 6 weeks for five (5) consecutive injections (baseline (BL), Weeks 6, 12, 18 and 24). To preserve the masking, the patients assigned to this regimen will receive sham injection on Weeks 4, 8 and 16.

Aflibercept: In the loading phase, treatment with aflibercept will occur every 4 weeks for five (5) consecutive injections (BL, Weeks 4, 8, 12 and 16). To preserve the masking, the patients assigned to aflibercept Arm will receive sham injection on Weeks 6 and 18.

Maintenance Phase

The treatment intervals during the maintenance phase will be as follows:

Brolucizumab 6 mg:

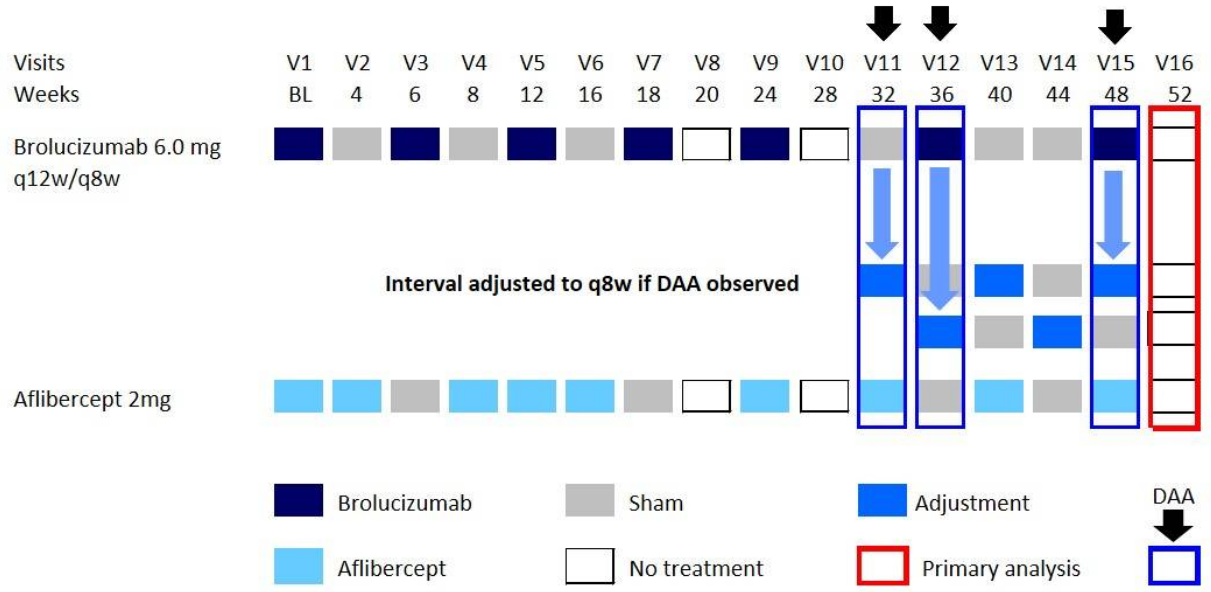
- From Week 24 onwards, patients will be scheduled to receive one injection of brolucizumab 6 mg every 12 weeks. At Weeks 32 and 36, DAA (Disease Activity Assessment) will be performed. If, however, Disease Activity is identified by the evaluating/masked investigator at Weeks 32 or 36, the patient will be assigned to receive treatment every 8 weeks (see Evaluation of Disease Activity below). DAA will be performed at Week 36 independently from the outcome of DAA performed at Week 32.
  An additional DAA will be performed at Week 48 to document the adequacy of the q12w treatment schedule at the end of the study (without having impact on the patient's treatment schedule).

Aflibercept 2 mg:

- From Week 16 onwards, patients will receive one injection of aflibercept 2 mg every 8 weeks (first injection after Week 16 to be given at Week 24) until Week 48 visit. DAAs will be conducted by the evaluating/masked investigator for masking purposes and will not influence the treatment interval.

[redacted]

Figure 6-1 Treatment schedule



DAA: Disease Activity Assessment

Evaluation of Disease Activity:

The concept of the brolucizumab q12w/q8w regimen is to allocate patients according to their individual treatment needs to either a q12w or a q8w treatment schedule. The initial schedule is q12w and a patient will remain on q12w as long as the masked investigator does not identify DME disease activity which in his opinion requires more frequent anti-VEGF treatment. However, the DAA and the decision by the investigator to adjust the treatment frequency only occur in pre-specified DAA-visits. To ensure identification of patients with higher treatment need early on, a closer monitoring of patients' individual treatment need will take place during the first q12w treatment interval with DAAs at Week 32 and 36 (i.e. for brolucizumab patients, 8 and 12 weeks after the last loading injection).

The assessment of the disease activity is at the discretion of the masked investigator and should be made based on changes in vision and anatomical parameters with reference to the patients' disease status at the time of Week 28. The outcome of this assessment will be captured as:

- 'q8w-need': identified disease activity which according to the masked investigator requires more frequent anti-VEGF treatment, e.g.: ≥5 letters loss in BCVA (compared to Week 28) which - based on anatomical parameters – is attributable to DME disease activity.
- 'no q8w-need': otherwise (no signs of disease activity)

If DAA reveals a need for more frequent treatment in brolucizumab patients, they will be assigned to receive brolucizumab injections at q8w intervals thereafter, up to the end of the study. Aflibercept patients will receive maintenance treatment every 8 weeks, regardless of the outcome of the Disease Activity Assessment as per approved regimen. Only assessments at scheduled treatment visits might have an impact on the patient's treatment schedule.

[redacted]

Missing DAA:

A patient who misses Week 32 (Visit 11) will undergo the disease activity assessment at Week 36 (Visit 12) as he/she would have done if the visit had not been missed. If, however, a patient misses the DAA planned on Week 36 visit, then the patient (brolucizumab arm only) will be assumed to have had a 'q8w-need' at this missed visit and will be assigned to a q8w schedule at the next visit (i.e. at the next visit the patient will receive an active injection) up to study exit. The IRT system will make the necessary changes once the missed visit is registered. If a patient misses the DAA planned on Week 48 (Visit 15) visit then the patient (brolucizumab arm only) will be assumed to have had a 'q8w-need' at this missed visit.

If a patient misses Week 28 (Visit 10), then the Week 24 (Visit 9) values should be applied as the reference for disease activity assessments.

Masking:

In order to maintain masking, the assessment of disease activity is conducted on all patients. The assessment of the masked/evaluating investigator will be passed to the unmasked/treating investigator or delegate in order to obtain the applicable treatment, active or sham, as assigned by IRT depending on the treatment arm and the actual treatment frequency as described above.

At all applicable visits from Week 4 to Week 48, inclusive (with exception of Weeks 20 and 28 where no treatment is scheduled), a sham treatment will be performed to maintain patient masking. For the sham treatment the tip of an injection syringe (the hub without a needle) will be used.

IVT injection procedure:

The IVT injection procedure for brolucizumab and aflibercept, including aseptic and antimicrobial requirements, will be performed according to local clinical practice. The sham injection should mimic an IVT injection including the aseptic and antimicrobial requirements. The tip of the sham injection syringe (the hub without a needle) will be placed on the eye for the approximate amount of time it would take to perform an IVT injection. IVT injection will be performed by the unmasked investigator.

IVT injection is contraindicated in patients with active ocular or periocular infections and in patients with active intraocular inflammation (IOI); therefore, the investigators **must** verify that these conditions are not present in the study eye prior to every injection.
If any signs of intraocular inflammation are present, then an IVT injection **must not** be performed. Additional ophthalmic examination and imaging should be performed to evaluate IOI (see Section 8.4.3).
If IOI is confirmed, subjects should be treated for IOI according to clinical practice and closely monitored since they may be at risk of developing retinal vasculitis and/or retinal vascular occlusion. If subject develops retinal vasculitis and/or retinal vascular occlusion based on the investigator's evaluation, the study treatment must be discontinued.

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.

[redacted]

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.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Good Clinical Practice (ICH GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (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 safety finding. As new information becomes available, informed consent to be updated and then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and for 3 months after stopping the investigational medication and agree that in order to participate in the study they must adhere to the contraception requirements.

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

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

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 subject and person obtaining informed consent, etc.). Remote informed consent should be appropriately documented and confirmed by way of standard informed consent procedures at the earliest opportunity when the subject will be back at the trial sites.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patients' source documentation.

[redacted]

Patients must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed.

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

Table 8-1 Assessment Schedule

Period	Screening	Treatment																	Follow-up Period
Visit Name	**Screening / Visit 0**	**Baseline / Visit 1**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**9b**	**10**	**11**	**12**	**13**	**14**	**15/EOT[2]**	**16 / EOS[3]**
Days	**-14 to -1**	**1**	**2**	**29**	**43**	**57**	**85**	**113**	**127**	**141**	**169**	**169 +1**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Weeks	**-2 to -1**	**1**	**1**	**4**	**6**	**8**	**12**	**16**	**18**	**20**	**24**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Demography	X																		
Informed consent[4]	X																		
Medical history/current medical conditions	X																		
Physical Examination[5]	X																		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion / Exclusion criteria	X	X																	
Visual Function Questionnaire-25		X											X						X
Vital Signs	X[6]	X[6]		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Pregnancy Test (serum)[7]	X																		X
Pregnancy test (urine)[7]		X		X		X	X	X		X	X		X	X	X	X	X	X	
Pharmacokinetics Informed Consent	X																		
Anti-drug antibody (ADA) blood collection	X			X			X				X				X				X
PK blood collection[8]			X									X							
Hematology	X						X												
Clinical Chemistry	X						X				X				X				X
Urinalysis	X						X												X
Best corrected visual acuity	X[9]	X[9]		X	X	X	X	X	X	X	X		X[9]	X	X	X	X	X	X[9]
Intraocular Pressure (IOP)	X[9]	X		X	X	X	X	X	X	X	X		X[9]	X	X	X	X	X	X[9]
Ophthalmic Exam[1, 10]	X[9]	X		X	X	X	X	X	X	X	X		X[9]	X	X	X	X	X	X[9]

[redacted]

Period	**Screening**	**Treatment**																	**Follow-up Period**
Visit Name	**Screening / Visit 0**	**Baseline / Visit 1**	**1b**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**9b**	**10**	**11**	**12**	**13**	**14**	**15/EOT[2]**	**16 / EOS[3]**
Days	**-14 to -1**	**1**	**2**	**29**	**43**	**57**	**85**	**113**	**127**	**141**	**169**	**169 +1**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Weeks	**-2 to -1**	**1**	**1**	**4**	**6**	**8**	**12**	**16**	**18**	**20**	**24**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Spectral Domain Optical Coherence Tomography[1]	X[9]	X		X	X	X	X	X	X	X	X		X[9]	X	X	X	X	X	X[9]
Color fundus photo (7-field) [1]	X[9]												X						X[9]
Fluoroscein angiography[1]	X[9]												X						X[9]
[redacted]																			
Disease activity assessment														X	X			X	
Contact IRT	X	X[12]		X	X	X	X	X	X		X			X	X	X	X	X	
Study drug or sham administration		X		X	X	X	X	X	X		X			X	X	X	X	X	

X Assessment to be recorded in the clinical database or received electronically from a vendor
[1] Additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation.
[2] EOT: End of treatment
[3] End of Study (EOS): All exit procedures should be followed, regardless of when the patient exits the study. Visit should be at least 4 weeks from last dose of study treatment. Patient report outcome (PRO) will not be administered on EOS if different from Week 52 visit.
[4] Must be signed/dated prior to performing any study procedures
[5] At Visit 1, significant findings present prior to the study start (or known to being started before) must be recorded in the relevant Medical History; and any changes during the study which meet the definition of an Adverse Event must be recorded as an Adverse Event
[6] In case there is an elevated blood pressure measurement as specified in the exclusion criteria, at screening or baseline visits, the blood pressure measurement should be repeated after 20 minutes. If the repeat measurement is elevated, then the patient is not eligible to be enrolled into the study.
[7] Women of childbearing potential only
[8] If PK Consent was provided
[9] Both eyes
[10] Includes fundus and slit lamp examination according to local practice.
[redacted]
[12] Patients will be randomized to brolucizumab 6 mg/50 µL or aflibercept 2 mg/50 µL

[redacted]

8.1 Screening

Screening

A screening period of up to 2 weeks will be used to assess eligibility.

One time rescreening of patients is allowed, except for the purpose of capturing new BCVA or imaging assessments that previously failed to qualify the patient. As long as testing can be repeated within 14 days of the first screening, the other screening assessments do not need to be repeated. If rescreening is to occur beyond 14 days from the original screening visit date, then all screening procedures must be repeated. Medical judgment should be exercised to ensure that treatment of DME is not withheld in order for a patient to participate in the study.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form (CRF). The demographic information, informed consent, Inclusion/Exclusion, and Disposition CRF 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 (SAE) during the screening phase (see Section 10.1.3). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail 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

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

- Age
- Gender
- Race
- Type of diabetes
- Vital signs
- Study eye
- Best corrected visual acuity
- Macular edema characteristics
- Intraocular pressure
- HbA1c and other laboratory test results
- Concomitant medications
- Medical history/current medical conditions

[redacted]

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

8.3 Efficacy

The following tests will be performed to assess activity of brolucizumab and aflibercept on visual function, retinal structure and leakage:

- Best-corrected visual acuity with ETDRS-like chart at 4 meters
- Anatomical markers on Spectral Domain Optical Coherence Tomography
- ETDRS DRSS score based on 7-field stereo Color Fundus Photography
- Vascular leakage evaluation by fluorescein angiography

All efficacy assessments should be performed prior to any administration of study treatment and/or rescue medication.

8.3.1 Visual acuity

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

8.3.2 Optical coherence tomography

Spectral domain optical coherence tomography (SD-OCT) will be assessed in the study eye at every study visit and in both eyes at Screening, Week 28 and Week 52 (EOS) visits.

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

[redacted]

The images will be reviewed by a CRC to ensure a standardized evaluation. For further procedural details, the investigator should refer to applicable manual provided by the CRC.

8.3.3 Color fundus photography and fluorescein angiography

Color fundus photography and fluorescein angiography will be performed in the study eye at Week 28 visit, and in both eyes at Screening and Week 52 (EOS) visits. In case of premature termination there is no need to repeat the color fundus photography and fluorescein angiography if there was color fundus photography and fluorescein angiography within the previous 12

[redacted]

weeks, except if there is significant worsening of DME disease, in the opinion of the investigator.

[redacted]

These assessments will be performed by a trained technician at the sites and should be performed prior to any study drug administration. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects. The images will be reviewed by a CRC to ensure a standardized evaluation. Grading for DRSS will be performed at the CRC. For further procedural details, the investigator should refer to applicable manual provided by the CRC.

Additional images will be taken in case of any signs of intraocular inflammation. OCT, Color fundus photography and fluorescein angiography (preferably, [redacted] or with peripheral sweeps) should be performed for safety evaluation as described in Section 8.4.3.

8.3.4 Appropriateness of efficacy assessments

BCVA as a measure of retinal function as well as SD-OCT images to analyze anatomical changes are standard assessments to monitor DME and potential treatment effects in routine practice and clinical trials. Likewise established is FA that helps classifying the type of macular edema and is used to assess vascular leakage. ETDRS DRSS assessed via color fundus photography is standardized evaluation on the severity of diabetic retinopathy. This grading informs about the severity of the diabetic retinopathy underlying the macular edema. It was shown that anti-VEGF can improve the severity of the retinopathy the implications for the course of the edema and its treatment are currently being investigated.

8.4 Safety

Safety assessments will include physical examination, vital signs, height and weight, ophthalmic examinations, laboratory evaluation as well as monitoring and recording type, frequency, and severity for all AEs.

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, Section 10.1.1 refers to the AE section.

If the COVID-19 pandemic limits or prevents on-site study visits, phone calls or virtual contacts should be conducted for safety monitoring and discussion of the subject´s health status, until the subject can again visit the site.

[redacted]

Table 8-2 Assessments & Specifications

Assessment	Specification
Physical examination	A routine physical examination will be performed at screening and at EOS visit and include the examination of general appearance (e.g. skin, neck, lymph nodes, extremities, vascular and neurological). Information for all physical examinations will be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the eCRF capturing Medical History. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded on the appropriate AE eCRF page.
Vital signs	Sitting blood pressure and pulse rate will be collected at all visits before treatment Vital signs include assessment of sitting blood pressure (systolic and diastolic pressure in mmHg) and pulse (beats per minute). In case there is an elevated blood pressure measurement as specified in the exclusion criteria, at the screening or baseline visits, the blood pressure measurement should be repeated. If the repeat measurement is elevated, then the patient is not eligible to be enrolled into the study. On days when study drug is administered, vital signs will be measured **before** administration of study medication. The results will be recorded in the eCRF.
Height and weight	Height and weight will be measured at the screening visit only as part of the physical examination. Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg), in indoor clothing but without shoes) will be measured at screening only. The results will be recorded in the eCRF.

8.4.1 Laboratory evaluations

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

Clinically notable laboratory values are defined in Table 16-1 of Appendix 1.

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 communicated to the Investigator.

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, and basophils), and quantitative platelet count.
Clinical Chemistry	• Glycosylated hemoglobin (HbA1c) • Serum biochemistry tests Serum electrolytes (sodium, potassium, chloride, phosphorus, calcium), uric acid, urea nitrogen, creatinine, albumin, glucose, total protein, total bilirubin and direct bilirubin, SGOT (AST), SGPT (ALT), GGT, alkaline phosphatase, and LDH • Additional chemistry tests: Lipids panel (TG, LDL, HDL, TC)
Urinalysis	Dipstick measurements for specific gravity, pH, protein, glucose, ketones, bilirubin, nitrite, leucocyte and urine occult blood.

8.4.2 Pregnancy and assessments of fertility

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

[redacted]

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

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

In the absence of the above medical documentation, Follicle Stimulating Hormone (FSH) testing is required of any female subject, regardless of reported reproductive/menopausal status at screening/baseline.

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 serum pregnancy test will be conducted for all women of childbearing potential to assess pregnancy before inclusion into the study at screening visit and then at Week 52 (EOS) visit. During study, monthly urine pregnancy testing will be performed and results captured in the source documents

8.4.3 Other safety evaluations

The ophthalmic examination will consist of the following:

- **Biomicroscopy (slit lamp examination)** will be completed at every (scheduled and unscheduled) visit to examine the anterior segment structures (e.g., eyelids/lashes, conjunctiva, cornea, anterior chamber, iris, lens and anterior part of the vitreous) of the study eye (fellow eye will be examined only at Screening, Week 28, Week 52 (EOS) and on discretion of the investigator). The outcome of the examination will be recorded in the source documents.

  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.

  Any clinically significant abnormalities should be recorded in the adverse event page of the eCRF (events identified at the time prior to signing the ICF should be recorded in the medical history page).
- **Intraocular pressure** will be assessed in the study eye, pre-dose and post-dose at every scheduled visit. In the fellow eye, IOP will be assessed at screening, Week 28, and Week 52 (EOS). The values recorded in mmHg will be entered into the eCRF. Treatment and close monitoring of IOP should be performed by the masked investigator for any non-transient elevation in intraocular pressure (≥25 mmHg). Intravitreal procedure is not recommended unless normalization of the IOP has been achieved. Post-dose IOP should be assessed within 60 minutes after every IVT/Sham injection and if ≥25 mmHg, the assessment should be repeated until the IOP comes back to normal. Any clinically significant abnormalities deemed by the investigator as adverse event, should be recorded on the adverse event page of the eCRF (events identified at the time prior to signing the ICF should be recorded on the medical history page).

[redacted]

- **Posterior segment (indirect fundus) examination** will be conducted by the masked investigator at the screening visit for both eyes. An examination of the peripheral retina must also be conducted to ensure that the intravitreal injection can safely be performed. Posterior segment examination must be performed carefully before each study treatment. The results of the examination including any abnormalities (e.g. vitreous cells/haze, retinal tear/detachment, hemorrhage and vascular occlusion, vasculitis, etc.) should be recorded in the source documents. If there are any signs of IOI, vitreous cells and haze should be assessed using National Institutes of Health (NIH) grading system (Nussenblatt et al., 1985). The outcome of the examination will be documented in the source document (e.g., ophthalmic examination tool) and appropriate eCRF page as applicable. Any clinically significant abnormalities of either eye should be recorded in the medical/ocular history page prior to signing the ICF and in the adverse event page of the eCRF for any findings identified after signing the ICF.
- **Instruct the patient to contact the site for any changes in vision or any symptoms of inflammation between scheduled visits.** Every effort should be made to bring the subject for immediate examination. When IOI, retinal vasculitis, and/or Retinal Artery Occlusion (RAO) is present or suspected during a visit, investigators must perform thorough ophthalmic examination, and will conduct OCT, fluorescein angiography and color fundus photography (preferably [redacted] with peripheral sweeps). These additional assessments will be documented in the source and appropriate eCRF pages as applicable. The images are requested to be uploaded onto the CRC portal. If subject develops retinal vasculitis and/or retinal vascular occlusion based on the investigator's evaluation, the study treatment must be discontinued. In addition, as some of the subjects who experience IOI may be at the risk of developing retinal vasculitis and/or retinal vascular occlusion, the subject should be closely monitored and managed according to clinical practice.

8.4.4 Appropriateness of safety measurements

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

8.5 Additional assessments

Additional assessments that will be performed:

- Patient Reported Outcome: National Eye Institute (NEI) VFQ-25
- Pharmacokinetics (PK) of brolucizumab
- Anti-Drug Antibodies (ADA) of brolucizumab

8.5.1 Clinical Outcome Assessments (COAs)

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

[redacted]

conditions. This allowed the developers to identify the content areas and aspects of visual disability that were most important and relevant to AMD patients. In addition to its use in measuring the treatment effect on vision-related function in AMD patients, the NEI VFQ-25 has been used to measure treatment benefits in subjects with DME (Klein et al 2001).

At baseline, Weeks 28, and 52, the NEI VFQ-25 will be completed and captured by masked site staff on behalf of the subjects, at sites where local language versions are available, validated, and approved by the IEC/IRB. All these questionnaires should be completed before completing any other study procedures of the visit. The time of the day that the questionnaire was completed must be recorded in the subject's source documents. Answers to NEI VFQ-25 will be captured electronically independently from the eCRF (in a dedicated database). The subject's answer to the interview questions will be reviewed and examined by masked site staff and recorded in the source documents.

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

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

8.5.2 Pharmacokinetics

Serum PK samples will be collected on approximately 24 consented patients to obtain approximately 12 patients in brolucizumab arm for systemic exposure assessment (around 12 patients per treatment arm to maintain masking, samples from patients who received aflibercept will not be analyzed). Serum samples will be taken at 2 time points:

- Approximately 24 hours after the first dose at Baseline
- Approximately 24 hours after the treatment at Week 24

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

8.5.3 Other Assessments

Anti-drug antibodies (immunogenicity):

Anti-drug antibodies (ADAs) assessment will be done at screening, Weeks 4, 12, 24, 36 and 52 (EOS) visit in subjects treated with brolucizumab only (collection of ADA samples will be done in both treatment arms to maintain masking, samples from subjects in aflibercept arm will not be analyzed). Systemic exposure of brolucizumab will be measured concomitantly with ADA levels for interpretation purposes only. Blood draws should take place prior to the injection/sham. A standardized procedure for the collection, processing, storage and shipment of these blood samples is provided by the central laboratory. Further details on sample collection, numbering, processing and shipment can be found in the central laboratory manual. Additional pharmacodynamic assessment may be conducted on the samples wherever permitted by local regulation.

9 Study discontinuation and completion

9.1 Discontinuation

The investigator should discontinue study treatment for a given patient and/or withdraw the patient from study if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

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

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

9.1.1 Discontinuation of study treatment

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

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

Study treatment must be discontinued under the following circumstances:

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

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

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent Section 9.1.2). **Where possible, they should return for the assessments indicated** in the assessment schedule until the EOS visit. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

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

- new / concomitant treatments

[redacted]

- adverse events/Serious Adverse Events

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

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

9.1.1.1 Replacement policy

Discontinued subjects will not be replaced.

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

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent/opposition to use data/biological samples occurs only when a subject:

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

and

- No longer wishes to receive study treatment

and

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

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

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

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

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table (Table 8-1).

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

[redacted]

For China: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed.

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

In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible 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 EOS 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 subjects who are prematurely withdrawn from the study.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a 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.

[redacted]

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

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

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

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

1. The severity grade.
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities
2. its relationship to the study treatment or the intraocular injection procedure. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment.

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

- Dose not changed
- 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)

6. its outcome:
    a. not recovered/not resolved;
    b. recovered/resolved;
    c. recovered/resolved with sequelae;
    d. fatal;
    e. unknown.

[redacted]

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 administration of study treatment.

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

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

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease. Investigators have the responsibility for managing the safety of individual subjects and identifying adverse events. Clinically notable laboratory values 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 a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

[redacted]

  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization 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.

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 and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

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

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.

[redacted]

10.1.4 Pregnancy reporting

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 Chief Medical Office and Patient Safety (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 with any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors

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

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

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

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

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

11 Data Collection and Database management

11.1 Data collection

Designated masked investigator staff will enter the data required by the protocol into the electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulation (CFR) Part 11

[redacted]

requirements, Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

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

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

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

11.2 Database management and quality control

Novartis personnel (or designated Contract Research Organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated masked 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 World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis. Color fundus photographs, fluorescein angiograms, and OCT images will be processed centrally by the Central Reading Center and the results will be sent electronically to Novartis.

The data management staff will perform a reconciliation of the data entered on the eCRF versus what is received from the central reading center and central labs. At a minimum, this reconciliation will include header reconciliation, visit window checks, duplicate record checks, out of range checks as defined by the Clinical Trial Team (CTT) and checks to address missing reading center data and missing central lab data.

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

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

The occurrence of relevant protocol deviations (PDs) will be determined. Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unmasked** and made available for data

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

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, retinal images, 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 study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The primary safety and efficacy analysis will be based on the Week 52 data, i.e. all data up to and including Week 52.

Summary statistics will be presented by treatment group unless otherwise specified. For continuous variables, summary statistics will generally include: n, mean, standard deviation, median, quartiles, minimum, and maximum. For categorical variables, this will generally include: n, frequency and percentage in each category.

Further technical details and discussions of the statistical considerations will be provided in the statistical analysis plan (SAP).

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

[redacted]

Additional analysis populations may be defined and sensitivity analyses may be conducted to evaluate the impact of COVID-19 pandemic.

12.1 Analysis sets

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

The **Full Analysis Set** (FAS) will include all randomized patients who receive at least one IVT injection of the study treatment. The full analysis set will serve as the primary analysis set for all efficacy analyses. Following the intent-to-treat principle, patients will be analyzed according to the treatment assigned to at randomization.

Supportive analyses of the primary and key secondary endpoints will include analysis using the **Per Protocol Set** (PPS). PPS is a subset of the FAS and will exclude patients with protocol deviations (PDs) and analysis restrictions (ARs) that are expected to majorly affect the validity of the assessment of efficacy at Week 52 including for e.g. lack of compliance (including missed treatments and treatment misallocation), missing data, prohibited concomitant medication and deviation from inclusion/exclusion criteria. Confounded data or discontinuation from treatment due to lack of efficacy and/or safety do not constitute a reason for exclusion from the PPS.

Before the Week 52 database lock the relevant protocol deviations will be identified at the patient level in the database. After the Week 52 database lock, analysis restrictions will be derived in the analysis database. Censoring applied in relation to the specific PDs / ARs will be specified as well.

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

The **Safety Analysis Set** (SAF) will include all patients who receive at least one IVT injection of the study drug. Patients in the safety analysis set will be analyzed according to the treatment arm from which they received majority of treatments up to and including Week 48.

12.2 Subject demographics and other baseline characteristics

Demographics and baseline characteristics will be summarized with descriptive statistics for the FAS by treatment group and overall.

Relevant medical history/current medical conditions will be tabulated by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary for the FAS.Other relevant baseline information will be listed and summarized with descriptive statistics as appropriate.

12.3 Treatments

Study treatment

[redacted]

Descriptive statistics for exposure to study treatment will be provided for the Safety set, FAS and PPS. For the efficacy analysis sets (FAS and PPS), the number of active and sham IVT injections will be presented by visit and cumulatively for the period baseline to Week 48, including separate analysis for the loading phases, i.e. up to Week 16 (last treatment of the 5*q4w loading of aflibercept) and up to Week 24 (last treatment of 5*q6w loading of brolucizumab), and maintenance phase. For the safety analysis set, summary will include exposure data up to Week 52.

Prior medication and concomitant therapies

The number and percentage of patients taking prior medication or concomitant therapies will be summarized by preferred term according to the WHO Drug Reference List dictionary using the Safety Set and FAS (in case there are differences between those two). The concomitant therapies (medications and procedures) will include all therapies received after start of study treatment including those already started prior to the start of study treatment.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The primary endpoint is the change from baseline in BCVA at Week 52.

The first key secondary endpoint is average change in BCVA from baseline over the period Week 40 through Week 52. For each patient, this endpoint is defined as the average of the changes from baseline to Weeks 40, 44, 48 and 52. The motivation for the choice of this endpoint is that, averaging the BCVA values over Week 40 to Week 52 will account for both random fluctuations and potential trough and peak values during the different treatment cycles. During the period Week 40 to Week 52, aflibercept and brolucizumab patients on q8w will have two assessments 4 weeks after the last dose, and two assessments 8 weeks after the last dose. Brolucizumab patients on a q12w regimen will have two assessments 4 weeks after the last dose, one assessment 8 weeks after the last dose, and one assessment 12 weeks after the last dose.

The primary analysis of the primary and first key secondary endpoints will be based on the FAS.

12.4.2 Statistical model, hypothesis, and method of analysis

The objective related to the primary and first key secondary endpoints is to demonstrate non-inferiority of brolucizumab to aflibercept with respect to change from baseline in BCVA, considering a margin of 4 ETDRS letters.

Let:

B = Brolucizumab 6 mg - 5 x q6w loading then q12w/q8w maintenance

A = Aflibercept 2 mg - 5 x q4w loading then q8w maintenance

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

$\mathbf{H0_1}$: $\mu_B - \mu_A \leq -4$ letters vs. $\mathbf{HA_1}$: $\mu_B - \mu_A > -4$ letters

$\mathbf{H0_2}$: $\varphi_B - \varphi_A \leq -4$ letters vs. $\mathbf{HA_2}$: $\varphi_B - \varphi_A > -4$ letters

[redacted]

where μ_B and μ_A are the corresponding unknown true mean changes from baseline in BCVA at Week 52; φ_B and φ_A are the corresponding unknown true mean changes from baseline in BCVA averaged over the period Week 40 to Week 52;

Based on the FAS, the above hypotheses will be tested via an analysis of variance (ANOVA) model. The model will include treatment, baseline BCVA (≤65, >65 letters) and age category (<65, ≥65 years) as factors. Two-sided 95% confidence interval (CI) for the least square means difference (brolucizumab - aflibercept) will be presented. Non-inferiority will be considered established if the lower limit of the corresponding 95% CI is greater than -4 letters.

These two hypotheses will be tested sequentially in the order of their numbering (HAn, n=1, 2). Consequently, confirmatory testing of the second hypothesis requires rejection of the first null hypothesis.

In this setting, each hypothesis will be assessed at a one-sided significance level of 0.025, while keeping the global type I error rate at 0.025.

12.4.3 Handling of missing values/censoring/discontinuations

Missing BCVA values will be imputed by LOCF (Last Observation Carried Forward) as a primary approach. For patients with no post-baseline BCVA value, the baseline value will be carried forward. Data collected after start of alternative DME treatment in the study eye (e.g. other anti-VEGF treatment, laser or intraocular corticosteroids, as further detailed in the SAP) will be censored for the primary analysis.

From an estimand perspective, the main focus is to adequately reflect in the analysis unfavorable study outcome related to the treatment (e.g. lack of efficacy, safety problems).

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

In case of missing data occurring independently of the response to study treatment, the LOCF approach assumes stability which seems to be adequate based on historical data both for the maintenance treatment phase (i.e. stabilization of BCVA) and also in case of the absence of any treatment effect with an average natural disease progression in terms of BCVA of only 1-2-letter loss over 1 year. In case of an early study termination during the loading phase, the LOCF method will result in a conservative estimate potentially underestimating the true outcome.

LOCF is an established method within the assessment of efficacy of anti-VEGF treatments in terms of BCVA outcome. Non-inferiority studies should follow the main design features (primary variables, the dose of the active comparator, eligibility criteria, etc.) as the previously conducted superiority trials in which the active comparator demonstrated clinically relevant efficacy. The primary endpoint in aflibercept Phase III studies VIVID and VISTA was the BCVA change from Baseline to Week 52 with missing data imputed based on LOCF. Based on

[redacted]

those studies, the percentage of missing data regarding BCVA is not considered critical (<10%) which limits the impact of the missing data imputation method.

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

Table 12-1 Primary and supplementary estimands

Estimand	Estimand definition	Analysis set	Statistical methods (Including strategy for imputation of missing/censored data)
Primary estimand	Difference in change from baseline in BCVA at Week 52 excluding the effect of switching to alternative DME medication in the study eye	FAS	Analysis of variance (ANOVA) model including terms for treatment, baseline BCVA (≤65, >65 letters) and age category (<65, ≥65 years), and using LOCF imputation/replacement for missing/censored data.
Supplementary estimand	Difference in change from baseline in BCVA at Week 52 for patients adhering to the protocol as per the PPS definition	PPS	ANOVA model as per the primary estimand. LOCF imputation/replacement for missing/censored data

12.4.4 Sensitivity and Supportive analyses

Sensitivity and supportive analyses will be performed for primary and the first key secondary endpoints related to BCVA using the per protocol analysis set (PPS), alternative methods of handling missing values (Section 12.4.3) and descriptive analyses based on observed data only (with and without censoring of data collected after use of alternative treatment for DME in the study eye, e.g. other anti-VEGF treatment, laser, intraocular corticosteroids, as further detailed in the SAP).

The following subgroup analyses will be conducted in FAS applying the primary analysis approach as specified above:

- Age category (<65, ≥65 years)
- Gender (male, female)
- Diabetes type (Type 1, Type 2)
- Baseline HbA1c (<7.5, ≥7.5%)
- Baseline BCVA categories (≤65, >65 letters)
- Duration of DME (≤3, >3-<12, ≥12 months)
- DME type (focal, diffuse) as per CRC
- Baseline CSFT (<450, ≥450-<650, ≥650 µm)
- Baseline status of IRF (presence, absence)
- Baseline status of SRF (presence, absence)

Further description of the additional analyses will be detailed in the SAP.

[redacted]

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

12.5.1.1 Additional key secondary endpoints

Additional key secondary endpoints are:

- Proportion of patients maintained at q12w up to Week 52 (for brolucizumab treatment arm only)
- Proportion of patients maintained at q12w up to Week 52, within those patients that qualified for q12w at Week 36 (for brolucizumab treatment arm only)

The estimate for the proportion of patients with a positive q12w treatment status at Week 52 will be derived from Kaplan Meier time-to-event analyses for the event 'first q8w-need' applying a 'q8w-need' allocation in case of missing or confounded data attributable to lack of efficacy and/or lack of safety.

The proportion of patients with a positive q12w treatment status at Week 52 will be derived considering the q8w-need (reflecting duration of effect) and potential limitations in terms of efficacy and safety:

- Patients will need to have the status of 'q8w need = no' at Weeks 32, 36 and 48 unless the 'q8w need = yes' is confounded by reasons other than lack of efficacy and/or safety (see censoring details below)
- Potential limitations in terms of efficacy and safety will be addressed by considering patients – even without an explicit 'q8w need = yes' – as having a negative q12w status in case any of the following confounding factors is attributable to lack of efficacy and/or lack of safety of the study treatment (assessed based on a masked medical review): early treatment/study discontinuation, use of forbidden concomitant medications/procedures and/or other deviation from treatment schedule (e.g. due to a missed visit/treatment). The corresponding q8w need will be allocated to the next disease activity assessment visit following the occurrence of such a confounding factor

In case missing or confounded data regarding the q12w treatment status are attributable to reasons other than lack of efficacy and/or safety, the patient is censored within the q12w treatment status analysis according to the following specifications:

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

The details regarding handling of missing values and discontinuations including the timing of censoring within the time-to-event analyses for the event 'first q8w-need' are specified above.

[redacted]

From an estimand perspective, the assessment of failing study completion according to protocol due to lack of efficacy/safety is considered adequately represented by a negative q12w-status.

Alternative methods of handling missing or confounded data within sensitivity analyses will include an approach with 'q8w-need' allocation only in case of missing or confounded data attributable to lack of efficacy and an 'as observed' approach, i.e. an analysis without 'q8w-need' allocation.

Sensitivity analyses will be performed for additional key secondary endpoints using the per protocol analysis set (PPS), alternative methods of handling missing values (described above) and descriptive analyses based on observed data only (with and without censoring of data collected after use of alternative treatment for DME in the study eye, e.g. other anti-VEGF treatment, laser, intraocular corticosteroids, as further detailed in the SAP).

12.5.1.2 Other secondary endpoints

Summary statistics will be presented by treatment group using the FAS. For continuous variables, summary statistics will generally include: n, mean, standard deviation, median, quartiles, minimum, and maximum. For categorical variables, this will generally include: n, frequency and percentage in each category.

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

Secondary efficacy endpoints based on BCVA:

- Change from baseline in BCVA at each visit up to Week 52
- Average change from baseline in BCVA over the period Week 4 to Week 52.
- Average change from baseline in BCVA over the period Week 20 to Week 52 and Week 28 to Week 52
- Gain in BCVA of ≥5, ≥10 and ≥15 ETDRS letters from baseline to each post-baseline visit

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

- Time to achieve gain of ≥5, ≥10 and ≥15 ETDRS letters from baseline (or reaching a score of 84 or more)
- Loss in BCVA of ≥5, ≥10 and ≥15 ETDRS letters from baseline to each post-baseline visit
- Absolute BCVA ≥73 ETDRS letters at each post-baseline visit

Secondary efficacy endpoints related to dosing regimen:

- q8w treatment need status assessed at Week 32
- Treatment status at Week 52

Secondary efficacy endpoints related to anatomy:

- Change from baseline in central subfield thickness (CSFT, as determined by SD-OCT from the CRC) at each assessment visit
- Average change in CSFT from baseline over the period Week 40 through Week 52
- Average change in CSFT from baseline over the period Week 4 to Week 52

[redacted]

- Patient status regarding normal CSFT (<280 microns) at each assessment visit
- Proportion of patients with presence of SRF, IRF and simultaneous absence of SRF and IRF at each assessment visit
- Proportion of patients with presence of leakage on FA at Weeks 52

Secondary efficacy endpoints related to the status of Diabetic Retinopathy:

- Patient status regarding a ≥2- and ≥3-step improvement or worsening from baseline in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score at each assessment visit
- Incidence of progression to PDR as assessed by ETDRS-DRSS score of at least 61 by Week 52

12.5.2 Safety endpoints

Safety endpoints are based on the variables from safety assessments which include:

- Extent of exposure
- Adverse events
- Ophthalmic examinations
- Vital signs
- Laboratory results

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

Adverse events

A treatment-emergent adverse event is defined as any adverse event that develops after initiation of the study treatment or any event already present that worsens following exposure to the study treatment. Only treatment-emergent adverse events will be presented in the summary tables.

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

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

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

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

[redacted]

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

Ophthalmic examinations

Pre-injection IOP measurements will be presented descriptively (absolute values and change from baseline). Post-injection IOP measurements will be listed.

Laboratory tests, vital signs, and special tests

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

12.5.3 Pharmacokinetics

Serum concentration data of brolucizumab will be listed by patient, and visit/sampling time point. Pharmacokinetic parameters will not be calculated. For purposes of calculating mean concentration values at each time point a value equal to one-half the lower limit of quantification (LLOQ) will be used for any individual subject whose determined concentration value is below the limit of quantitation. If a majority of patients at any time point/group are found to be below the limit of quantitation or if the calculated mean concentration value is below the nominal limit of quantitation then the resultant mean concentration will instead be reported as below the limit of quantitation. Descriptive statistics of the concentration values at each time point will include arithmetic and geometric means, SD, median, minimum and maximum, as appropriate.

12.5.4 Patient reported outcomes

The NEI VFQ-25 questionnaires will be scored (total and subscale scores) at Baseline and Weeks 28 and 52. Absolute scores and the absolute changes from Baseline will be calculated and summarized descriptively.

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

12.5.5 Anti-drug antibodies

Collection of blood for ADA assessment will be done at Screening and weeks 4, 12, 24, 36, 52 (end of study visit, EOS) visit prior to the injection/sham.

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[redacted]

12.7 Interim analyses

Interim analyses are not planned in this study.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

A sample size of 120 patients per arm will allow to demonstrate a non-inferiority (NIM of 4 ETDRS letters) of brolucizumab 6 mg vs. aflibercept 2 mg with respect to the BCVA change from baseline at Week 52, with 80% power at a one-sided alpha level of 0.025, assuming equal means and a common standard deviation of 11 letters. Assuming that averaging over the 4 time points will not lead to an increase in the standard deviation a power of at least 80% can also be expected for its corresponding non-inferiority claim.

To account for a drop-out rate of 10%, a total of 268 (134 per arm) patients will need to be randomized.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov. In addition, after study completion 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.

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

[redacted]

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.

15 References

References are available upon request

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[redacted]

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values

Table 16-1 Clinically notable laboratory values

Panel/ Test	Type	Gender /Age	Conventional Unit	Conventional Low	Conventional High	SI Unit	SI Low	SI High	Non-numeric
Chemistry/ Calcium	alert	All	mg/dL	6.1	12.9	mmol/L	1.52	3.22	
Chemistry/ Creatinine	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	alert	All							Negative, inconclusive
Hematology/ Hematocrit	alert	All	%	18	60	%	18	60	
Hematology/ Hemoglobin	alert	All	g/dL	8	22	g/L	80	220	
Hematology/ Platelet	alert	All	K/cumm	30	900	$x10^9$/L	30	900	
Hematology/ WBC	alert	All	K/cumm	2	25	$x10^9$/L	2	25	

[redacted]