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Novartis Research and Development

RTH258 (Brolucizumab)

Clinical Trial Protocol CRTH258C2302 / NCT03810313

An Eighteen-Month, Two-Arm, Randomized, Double-Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Macular Edema secondary to Central Retinal Vein Occlusion (RAVEN)

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List of abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AMD	Age-related macular degeneration
ANOVA	Analysis of variance
AR	Analysis restriction
BCVA	Best-corrected visual acuity
BRVO	Branch retinal vein occlusion
CFR	Code of Federal Regulation
CMO & PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical outcome assessment
COVID-19	Coronavirus disease 2019
CP	Color fundus photography
CRC	Central Reading Center
CRVO	Central retinal vein occlusion
CSFT	Central subfield thickness
DDE	Direct data entry
DMC	Data Monitoring Committee
DME	Diabetic macular edema
[redacted]	[redacted]
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
ESI	Event of special interest
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAS	Full analysis set
FDA	Food and Drug Administration
g/dL	gram(s) per deciliter
GCP	Good Clinical Practice
GCS	Global Clinical Supply
hCG	Human chorionic gonadotropin
IB	Investigator's Brochure
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFT	Individualized flexible treatment
IOI	Intraocular inflammation
IOP	Intraocular pressure
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRF	Intraretinal fluid
IRT	Interactive Response Technology
IVT	Intravitreal injection
K/cu mm	thousand per cubic millimeter
kDA	kilo Dalton
LOCF	Last observation carried forward

[redacted]

ME	Macular edema
MedDRA	Medical dictionary for regulatory activities
mEq/L	milliequivalent(s) per liter
mg	milligram(s)
mL	milliliter(s)
mmHg	millimeter(s) of mercury
mmol/L	millimole(s) per liter
nAMD	Neovascular age-related macular degeneration
NEI	National Eye Institute
NIM	Non-inferiority margin
OCT	Optical coherence tomography
PD	Protocol deviation
PPS	Per Protocol Set/Protocol analysis set
PRO	Patient reported outcome
q12w	every 12 weeks
q4w	every 4 weeks
q8w	every 8 weeks
RAS	Randomized analysis set
RAO	Retinal artery occlusion
RoW	Rest of World
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
scFv	Single-chain fragment variable
SD-OCT	Spectral domain optical coherence tomography
SOP	Standard operating procedure
SRF	Subretinal fluid
SUSAR	Suspected Unexpected Serious Adverse Reaction
VA	Visual acuity
VEGF	Vascular endothelial growth factor
VFQ-25	Visual function questionnaire-25
WBC	White blood cell(s)
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biological samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve masking of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit
Electronic data capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
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/treatment	The study drug whose properties are being tested in the study
Masked/evaluating investigator	For the entire study duration and all study subjects, the masked/evaluating investigator is responsible for all aspects of the study (the conduct/supervision of all assessments and treatment decisions except the injection procedures and the safety assessment following the 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.
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.

[redacted]

Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts
Unmasked/treating investigator	For the entire study duration and all study subjects, the treating investigator only performs the treatment (injection active/sham) and assesses subject safety following the active/sham injections
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Visual acuity assessor	For the entire study duration and all study subjects, the visual acuity assessor (which could be a masked/evaluating investigator) performs the BCVA assessment and is masked to the assigned treatment
Withdrawal of Consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

[redacted]

Amendment 1 (08-Jun-2020)

Amendment rationale

[redacted]

Changes to the protocol

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

- Section 1.1 Background: Information was added to describe a 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 intravitreal injection **must not** be performed and patients should be treated for IOI according to clinical practice.
- Additional examination and assessments to fully characterize cases of intraocular inflammation were included in the following sections:
  - Table 8-1 Assessment schedule
  - [redacted]
  - Section 8.4.3 Ophthalmic 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
- Table 6-2 Prohibited medications/procedures
- Section 7 Informed consent procedures
- Section 8 Visit schedule and assessments
- Section 8.4 Safety
- Section 8.4.1 Laboratory evaluations
- Section 12 Data analysis and statistical methods

Other changes incorporated in this amendment:

- Section 6.1.1 Investigational and comparator drugs
- Section 6.2.1.1 Permitted concomitant therapy

[redacted]

- 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.
- [redacted]
- Section 8.4.3 Ophthalmic examination: Clarification was added for the use of the same method of intraocular pressure (IOP) measurement and the timing of post-dose IOP assessment.
- Section 8.5.3 Anti-drug antibodies (immunogenicity)
- Section 10.1.3 SAE reporting: Clarification of the SAE reporting period.
- [redacted]
- Section 12.1 Analysis sets: Modifications were made to include the importance of estimands per ICH E9(R1) guidance.
- Section 12.4.2 Statistical model, hypothesis, and method of analysis
- Section 12.4.4 Sensitivity and supplementary analyses
- 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 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.

Summary of previous amendments

None

[redacted]

Protocol summary

Protocol number	CRTH258C2302
Full title	An Eighteen-Month, Two-Arm, Randomized, Double-Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Macular Edema secondary to Central Retinal Vein Occlusion (RAVEN)
Brief title	Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Macular Edema secondary to Central Retinal Vein Occlusion
Sponsor and Clinical phase	Novartis Phase III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate the efficacy and safety of brolucizumab in the treatment of patients with macular edema (ME) secondary to central retinal vein occlusion (CRVO) and its potential to reduce the treatment burden for patients
Primary objective(s)	To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the change in best-corrected visual acuity (BCVA) from baseline up to Month 6
Secondary objectives	1. To assess the effect of brolucizumab as compared to aflibercept on BCVA 2. To evaluate the anatomical outcome with brolucizumab relative to aflibercept 3. To evaluate the treatment frequency with brolucizumab during the individualized flexible treatment (IFT) period relative to aflibercept 4. To assess the safety and tolerability of brolucizumab relative to aflibercept 5. To evaluate the effect of brolucizumab relative to aflibercept on patient-reported vision-related quality of life 6. To assess the immunogenicity of brolucizumab
[redacted]	
Study design	The study is an eighteen-month randomized, double-masked, multicenter, active-controlled, non-inferiority, 2-arm study in subjects with visual impairment due to ME secondary to CRVO. Subjects will be randomized in a 1:1 ratio to 1 of 2 treatment arms: • Brolucizumab 6 mg: 6 x every 4 weeks (q4w) followed by 48 weeks of individualized flexible treatment (IFT) from Week 24 onwards • Aflibercept 2 mg: 6 x q4w followed by 48 weeks of IFT from Week 24 onwards
Population	Approximately 938 adult patients will be screened (20% screening failure rate expected) so that approximately 750 patients (375 per arm, 10% dropout rate expected) will be randomized in a 1:1 ratio in approximately 160 centers worldwide. The maximum study duration for 1 subject is 80 weeks, including screening and safety follow-up.
Key inclusion criteria	• Signed informed consent must be obtained prior to participation in the study • Male or female patients ≥ 18 years of age at screening • Patients with visual impairment due to ME secondary to CRVO diagnosed < 6 months prior to screening; hemiretinal vein occlusion will be classified as CRVO (study eye) • Best-corrected visual acuity (BCVA) score between 78 and 23 letters, inclusive, using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing

[redacted]

	charts (approximate Snellen equivalent of 20/32 to 20/320) at both screening and baseline visit (study eye)
Key exclusion criteria	• Ocular conditions/disorders - structural damage of the fovea, vitreous hemorrhage, retinal vascular occlusion other than CRVO, retinal detachment, macular hole, or choroidal neovascularization of any cause, diabetic retinopathy (except mild non-proliferative) and diabetic macular edema (study eye) • Any active intraocular or periocular infection or active intraocular inflammation (study eye) • Uncontrolled glaucoma defined as intraocular pressure (IOP) > 25 mmHg on medication, or according to investigator's judgment, at screening or baseline (study eye) • Presence of amblyopia, amaurosis or ocular disorders in the fellow eye with BCVA < 20/200 at screening (except when due to conditions whose surgery may improve visual acuity) • Ocular treatments - Previous treatment with any anti-vascular endothelial growth factor (VEGF) drugs or investigational drugs, intraocular or periocular steroids, macular laser photocoagulation (focal/grid), vitreoretinal surgery (study eye)
Study treatment	Brolucizumab 6 mg/0.05 mL Aflibercept 2 mg/0.05 mL
Efficacy assessments	• Best-corrected visual acuity (BCVA) using ETDRS-like charts • Spectral Domain Optical Coherence Tomography (SD-OCT)
Other assessments	[redacted] • National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) vision-related quality of life instrument • Anti-Drug Antibodies (Immunogenicity) [redacted]
Key safety assessments	• Monitoring of Adverse Events • Ophthalmic examinations • Physical examinations • Vital signs • Laboratory assessments (hematology, clinical chemistry, urinalysis) • Pregnancy testing
Data analysis	The objective related to the primary endpoint is to demonstrate non-inferiority of brolucizumab versus aflibercept with respect to the change from baseline in BCVA at Week 24, assuming a non-inferiority margin of 4 ETDRS letters. An analysis of variance (ANOVA) model will be used to test non-inferiority. The model will include treatment, baseline BCVA (≤ 34, 34 - 55, ≥ 55 letters) and age category (< 65, ≥ 65) as factors. Additional factors may be included if deemed relevant. Non-inferiority will be considered established if the lower limit of the 95% confidence interval for the least square mean difference brolucizumab - aflibercept at Week 24 is greater than -4 letters. Summary statistics will be presented by treatment group unless otherwise specified. For continuous variables, summary statistics will generally include: n, mean, standard deviation, median, quartiles, minimum, and maximum. For categorical variables, these will generally include: n, frequency and percentage in each category. [redacted]
Key words	Central retinal vein occlusion, anti-VEGF, macular edema

[redacted]

1 Introduction

1.1 Background

Retinal vein occlusion (RVO) is the second most common retinal vascular permeability disorder after diabetic retinopathy and is a significant cause of visual impairment. The 5-year, 10-year and 15-year incidences of RVO have been estimated as 0.8, 1.6 and 2.3 per 100 persons, respectively (Klein et al 2000; Cugati et al 2006; Klein et al 2008). Macular edema (ME) is the most common cause of vision loss in patients with branch retinal vein occlusion (BRVO) or central retinal vein occlusion (CRVO). In an *in vivo* model, it has been demonstrated that vascular endothelial growth factor (VEGF) can increase vascular permeability (Aiello et al 1994) and that intraocular levels of VEGF in the eyes with RVO are elevated (Campochiaro et al 2009).

Previous and current available therapies

Until the approval of ranibizumab, the management of ME associated with RVO was largely based on the results from the Branch Vein Occlusion Study and the Central Vein Occlusion Study, where laser treatment was shown to be effective for visual acuity (VA) gain in patients with BRVO but not in those with CRVO (The Branch Vein Occlusion Study 1984; The Central Vein Occlusion Study 1995). Laser photocoagulation was then the standard of care in patients with BRVO despite many patients failing to gain vision but for vision loss associated with CRVO there was no proven effective therapy (Finkelstein 1996). Pharmacologic treatment of RVO began with the use of corticosteroids and the approval of the intravitreal dexamethasone sustained-release implant (Ozurdex®) by the Food and Drug Administration (FDA) in 2009 and the European Medicines Agency (EMA) in 2010 (Haller et al 2010).

More recently, anti-VEGF therapies have revolutionized the treatment of ME secondary to RVO and are currently the standard of care in this indication as VEGF is a major mediator for ME in RVO. The most commonly used VEGF inhibitors, i.e. bevacizumab (Avastin®), aflibercept (Eylea®) and ranibizumab (Lucentis®) have demonstrated compelling evidence for resolution of ME and improvement of VA subsequent to the treatment with an anti-VEGF (Rabena et al 2007; Campochiaro et al 2010; Clark et al 2016).

Ranibizumab (0.5 mg) was globally approved (2010 by the FDA, 2011 by the Committee on Herbal Medicinal Products (CHMP) and 2013 by the Pharmaceutical and Medical Devices Agency (PMDA)) for the treatment of ME due to BRVO and CRVO, based on the results of 2 Phase III studies (BRAVO for BRVO and CRUISE for CRVO) (Campochiaro et al 2010; Brown et al 2010). These studies showed that approximately 60% of BRVO and 48% of CRVO patients treated with monthly ranibizumab gained at least 15 letters of VA at 6 months, compared with 29% and 17% of those treated with sham, respectively. The VA gain was maintained on average until Month 12 using a pro re nata (PRN) treatment regimen, which was based on VA and anatomic parameters.

Aflibercept (2 mg) was approved for the treatment of ME following RVO at a global level (2014 by the FDA, 2015 by the CHMP and PMDA) based on the results of 3 Phase III studies: COPERNICUS and GALILEO for CRVO (Pielen et al 2017) and VIBRANT for BRVO (Clark et al 2016). In these studies, approximately 60% of CRVO patients treated with monthly aflibercept gained ≥ 15 letters from baseline versus 17% in the sham group. Approximately 53%

[redacted]

of BRVO patients treated with monthly aflibercept gained ≥ 15 letters from baseline versus 27% in the laser group.

Currently available anti-VEGF treatments require frequent regular intravitreal (IVT) injections which can be burdensome to patients and health care professionals. Therefore, an unmet medical need to reduce the treatment burden with an effective alternative still exists.

Brolucizumab

Brolucizumab, formerly known as RTH258 and ESBA1008, is a humanized single-chain fragment variable (scFv) that binds to VEGF-A (i.e. interferes with activation of VEGF-R1 and R2 on endothelial cells) with a molecular weight of ~26 kDa. It is 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 and prolong drug distribution to the target site of action, supporting longer effective control of disease activity. This could potentially translate into a more durable efficacy and a reduced treatment burden (number of injections) for the patient and health care professional.

Brolucizumab in nAMD

In a single ascending dose Phase I study (C-10-083), the median time until patients fulfilled protocol defined criteria for receipt of standard of care treatment was 30 days longer for brolucizumab 6 mg (P = 0.036) versus ranibizumab, with the maximum effect on best-corrected visual acuity (BCVA) and central subfield thickness (CSFT) reached on Week 6 for brolucizumab versus Week 4 for ranibizumab. In a separate repeat dosing Phase II study (C-12-006, OSPREY) comparing brolucizumab 6 mg (n = 44) every 8 weeks (q8w), then every 12 weeks (q12w) administration, i.e. administration every q8w and q12w, respectively, against aflibercept (q8w administration, n = 45), brolucizumab achieved comparable visual outcome during the loading and q8w phase, with a lower number of patients requiring additional rescue treatments (5 out of 44 versus 10 out of 45, 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 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 BCVA from baseline to Week 48 in both trials using a non-inferiority margin (NIM) of 4 letters. 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 (every 12 weeks) dosing interval following the loading phase (Baseline to Week 8) 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 6 mg achieved

[redacted]

superior reductions in 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 Oct-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®). Considering these events, the overall risk/benefit assessment remains positive.

Summary

Ranibizumab, aflibercept and brolucizumab all inhibit the activity of VEGF-A with all three having proven efficacy in the treatment of nAMD while both ranibizumab and aflibercept have also previously demonstrated efficacy in the treatment of patients with ME secondary to BRVO and CRVO. These findings support the evaluation of brolucizumab in RVO 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 CRVO 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 (HAWK and HARRIER) 48-week study results, which demonstrated:
  - Visual gains at Week 48 achieved with 56% (HAWK) and 51% (HARRIER) of patients treated following a q12w regimen after the loading phase
  - 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

Previous studies demonstrating efficacy with anti-VEGFs on CRVO combined with the evidence detailed above support a loading phase with a q4w (i.e. every 4 weeks) regimen followed by an individualized flexible treatment (IFT) regimen in the maintenance phase based on disease stability for brolucizumab, thus potentially reducing the injection burden.

These considerations support the initiation of a Phase III program to evaluate the efficacy and safety of brolucizumab in the treatment of patients with ME secondary to CRVO with the objective to evaluate the potential to reduce the treatment burden for patients.

[redacted]

1.2 Purpose

The purpose of this study is to demonstrate the efficacy and safety of brolucizumab in the treatment of patients with ME secondary to CRVO.

2 Objectives and endpoints

For the detailed description of the primary endpoint and its statistical analysis, please refer to Section 12.4. Details of the statistical analyses for secondary [redacted] endpoints will be provided in the Statistical Analysis Plan (SAP).

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the change in best-corrected visual acuity (BCVA) from baseline up to Month 6	• Change from baseline in BCVA at Week 24
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the effect of brolucizumab as compared to aflibercept on best-corrected visual acuity (BCVA)	• Change from baseline in BCVA averaged over Week 40 to Week 52 and Week 64 to Week 76 • Change from baseline in BCVA by visit up to Week 76 • Proportion of study eyes with a gain ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline • Proportion of study eyes with a loss ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline
• To evaluate the anatomical outcome with brolucizumab relative to aflibercept	• Change from baseline in central subfield thickness (CSFT) averaged over Week 40 to Week 52 and Week 64 to Week 76 • Change from baseline in CSFT by visit up to Week 76 • Proportion of study eyes with presence of retinal fluid (intra- and/or subretinal fluid) by visit up to Week 76 (derived from SD-OCT) • Proportion of study eyes with a CSFT < 300 µM by visit up to Week 76
• To evaluate the treatment frequency with brolucizumab during the individualized flexible treatment (IFT) period relative to aflibercept	• Number of injections between Week 24 and Week 52 and between Week 24 and Week 76 • Time to first re-treatment between Week 24 and Week 76
• To assess the safety and tolerability of brolucizumab relative to aflibercept	• Incidence of ocular and non-ocular AEs up to Week 52 and Week 76
• To evaluate the effect of brolucizumab relative to aflibercept on patient-reported vision-related quality of life	• Change from baseline in patient reported outcomes (NEI VFQ-25) at Week 24, Week 52 and Week 76
• To assess the immunogenicity of brolucizumab	• Anti-drug antibody status at baseline and Week 4, Week 12, Week 24, Week 36, Week 52 and Week 76

[redacted]

[redacted]

[redacted]

3 Study design

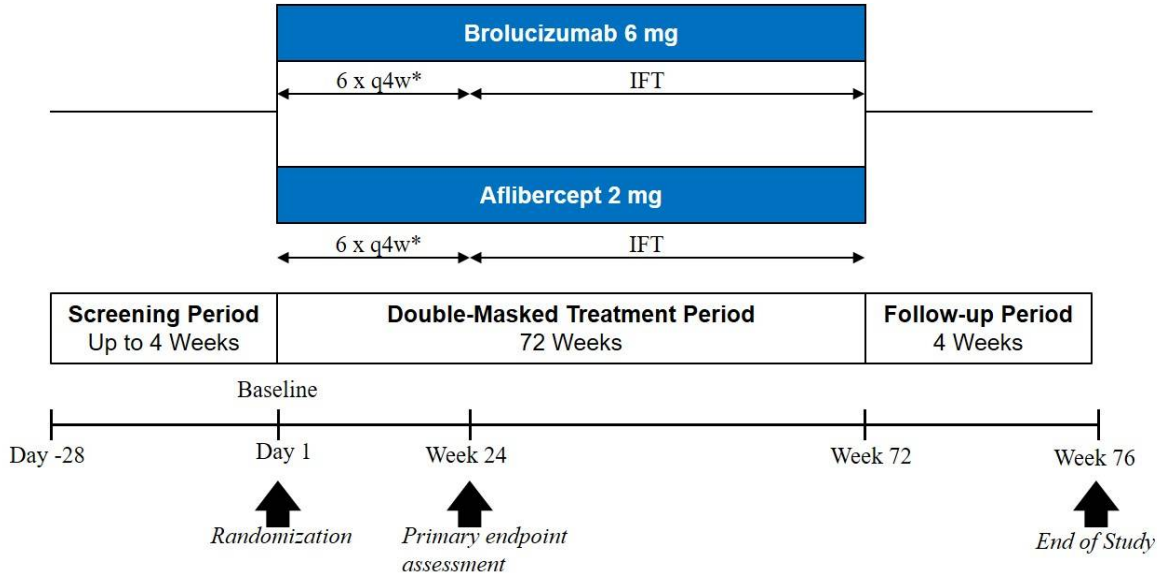
The study is an 18-month, randomized, double-masked, multicenter, active-controlled, non-inferiority, 2-arm study in subjects with visual impairment due to ME secondary to CRVO.

Patients who consent will undergo screening assessments to evaluate their eligibility based on the inclusion and exclusion criteria. Subjects who meet all the inclusion and none of the exclusion criteria will be randomized in a 1:1 ratio to 1 of 2 treatment arms:

- Brolucizumab 6 mg: 6 x q4w followed by 48 weeks of individualized flexible treatment (IFT) from Week 24 onwards
- Aflibercept 2 mg: 6 x q4w followed by 48 weeks of IFT from Week 24 onwards

Approximately 938 adult patients will be screened (20% screening failure rate expected) so that approximately 750 patients (375 per arm, 10% dropout rate expected) will be randomized in a 1:1 ratio in approximately 160 centers worldwide. The maximum study duration for 1 subject is 80 weeks, including screening and safety follow-up.

Figure 3-1 Study design



*Loading phase; IFT: Individualized flexible treatment

[redacted]

Screening period: Day -28 to Day -1

A screening period of up to 4 weeks will be used to assess subject eligibility.

One time reassessment of subjects is allowed, **except** for the purpose of capturing new BCVA assessments that previously failed to qualify the subject. 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 the subject must be reconsented and all screening procedures must be repeated. Medical judgment should be exercised to ensure that treatment of CRVO is not withheld in order for a subject to participate in the study.

Subjects must have confirmed ME secondary to CRVO at screening.

Double-masked treatment period: Day 1 to Week 72

After confirmation of eligibility, subjects will be randomized in a 1:1 ratio to one of the 2 treatment arms.

The baseline visit is defined as Baseline/Day 1, and end of treatment (EOT) visit as Week 72/Visit 19. The loading phase starts on Baseline/Day 1 and ends on Week 20/Visit 6. IFT starts on Week 24 until end of treatment (Week 72/Visit 19).

A study visit schedule will be established at the time of randomization for all subjects. All efforts should be made to adhere to this study visit schedule ±7□day window (except Baseline/Day 1). Treatment is intended to be administered on the day of study visit or, if this is not possible, within 3 days after the study visit when the per-protocol assessments took place (except for Baseline/Day 1, in which case study treatment administration should occur within the next 24 hours). However, 2 consecutive injections should be spaced by at least 21 days. In addition, for a given protocol visit (except Baseline/Day 1), assessments can be performed on 2 consecutive days in which both days must occur within the ±7-day window.

Post-treatment follow-up period: Week 72 to Week 76

For all subjects, the last study assessment will be performed at end of study (EOS) visit, Week 76/Visit 20, 4 weeks (±7 days) after the last potential study treatment in this study.

Subjects withdrawn from the study prior to study completion will be asked to return for an early discontinuation (EOS) visit, 4 weeks (±7 days) following their last study treatment administration.

4 Rationale

4.1 Rationale for study design

This study is designed as a multicenter, randomized, double-masked, 2-arm study to demonstrate the safety and efficacy of brolucizumab 6 mg compared to the active comparator, aflibercept, used in line with the authorized label. [redacted]

[redacted]

[redacted]

Masked treatment for 18 months (72 weeks) of treatment allows evaluation of the long-term safety and efficacy of brolucizumab in RVO compared to aflibercept.

[redacted]

Needleless sham intravitreal injections, i.e. imitation of an intravitreal injection procedure using an empty sterile syringe without a needle, were chosen instead of placebo intravitreal injections to avoid risk of ocular injury or endophthalmitis and because of ethical considerations.

4.2 Rationale for dose/regimen and duration of treatment

The dose 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 interval between injections during the IFT phase to reduce the treatment burden (see Section 1.1 for further details).

[redacted]

[redacted]

[redacted]

- Aflibercept is applied as permitted by the current labels in the EU and US.

Study duration (from Baseline/Day 1 to EOS visit) of 76 weeks is warranted to assess long term efficacy and safety of brolucizumab.

4.3 Rationale for choice of comparator

Aflibercept 2 mg is an established standard of care for RVO and has been chosen as an active comparator for this study due to the approved label of aflibercept (Eylea®) across many countries for the targeted indication as compared to other approved anti-VEGF treatments.

[redacted]

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 RVO, with benefits outweighing the risks. Assuming a corresponding class-effect, it is justified to expect that brolucizumab (having the same mechanism of action as ranibizumab and aflibercept) will likewise be efficacious and have a similar safety profile in the RVO indication.

In both Phase III studies (HAWK, HARRIER) in nAMD, brolucizumab demonstrated non-inferiority to aflibercept in mean change in BCVA from Baseline to Week 48. These results were achieved while a majority of patients on brolucizumab 6 mg – 56% in HAWK and 51% in HARRIER – were maintained on a q12w dosing interval following the loading phase through Week 48, i.e. with a reduced treatment frequency compared to aflibercept. Brolucizumab safety

[redacted]

was comparable to aflibercept, with the overall incidence of adverse events balanced across all treatment groups in both studies.

[redacted]

5 Population

The study population will be male and female patients ≥ 18 years old diagnosed with visual impairment due to ME secondary to CRVO. Approximately 938 patients will be screened (20% screening failure rate expected) and approximately 750 (375 per arm, 10% dropout rate expected) patients will be randomized in a 1:1 ratio in approximately 160 centers worldwide.

If both eyes are eligible as per the inclusion and exclusion criteria described below, the eye with the worse visual acuity should be selected for study eye, unless the investigator deems it more appropriate to select the eye with better visual acuity, based on medical reasons or local ethical requirements.

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. Male or female patients ≥ 18 years of age at screening

Study eye:

3. Patients with visual impairment due to ME secondary to CRVO diagnosed < 6 months prior to screening. Hemiretinal vein occlusion will be classified as CRVO for the purpose of this clinical trial.
4. BCVA score between 78 and 23 letters, inclusive, using ETDRS visual acuity testing charts (approximate Snellen equivalent of 20/32 to 20/320) at both screening and baseline

5.2 Exclusion criteria

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

Ocular conditions:

1. 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 during the first 12-month study period (e.g. structural damage of the fovea, vitreous hemorrhage, retinal vascular occlusion other than CRVO, retinal detachment, macular hole, or choroidal neovascularization of any cause, diabetic retinopathy (except mild non-proliferative) and diabetic macular edema)

[redacted]

2. 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
3. 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
4. Presence of amblyopia, amaurosis or ocular disorders in the fellow eye with BCVA < 20/200 at screening (except when due to conditions whose surgery may improve VA, e.g. cataract)

Ocular treatments:

5. Previous treatment with any anti-VEGF therapy or investigational drugs in the study eye at any time prior to baseline
6. Previous use of intraocular or periocular steroids in study eye at anytime prior to baseline
7. Macular laser photocoagulation (focal/grid) in the study eye at any time prior to baseline and peripheral laser photocoagulation in the study eye within 3 months prior to the baseline
8. Intraocular surgery in the study eye during the 3 month period prior to baseline
9. Vitreoretinal surgery in the study eye at any time prior to baseline
10. Aphakia with the absence of posterior capsule in the study eye

Systemic conditions or treatments:

11. Stroke or myocardial infarction during the 6-month period prior to baseline
12. End stage renal disease requiring dialysis or renal transplant
13. Uncontrolled blood pressure defined as a systolic value ≥ 160 mmHg or diastolic value ≥ 100 mmHg at screening or baseline. (In case there is an elevated blood pressure measurement, it should be repeated after 20 minutes. If the repeat measurement is elevated, then the patient is not eligible to be enrolled into the study)
14. Systemic anti-VEGF therapy during the 3-month period prior to baseline
15. 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, except temporary use for COVID-19 treatment
16. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar classes, or clinically relevant sensitivity to fluorescein dye as assessed by the investigator
17. 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
18. History of a medical condition (e.g. metabolic dysfunction disease 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
19. 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

[redacted]

longer or longer if required by local regulations (observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary)

Other:

20. 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
21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during the study drug administration and for 3 months after stopping the investigational medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking 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 6 weeks before taking study treatment. 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.

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.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and comparator drugs

Table 6-1 Investigational and comparator drug

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor
Brolucizumab 6 mg	Solution for injection	Intravitreal use	Glass vials or pre-filled syringe	Sponsor global
Comparator Drug	**Pharmaceutical Dosage Form**	**Route of Administration**	**Supply Type**	**Sponsor**
Aflibercept 2 mg	Solution for injection	Intravitreal use	Glass vials or prefilled syringe	Sponsor global

Brolucizumab will be provided in a single use, sterile glass vial, or may be provided in a pre-filled syringe (PFS) (in selected countries) containing sufficient brolucizumab to deliver a 6 mg dose when administering a volume of 0.05 mL.

Aflibercept will be provided in a single use, sterile glass vial, or may be provided in a pre-filled syringe (in selected countries) containing sufficient aflibercept to deliver a 2 mg dose when administering a volume of 0.05 mL.

The content of the study drug vials must **not** be split.

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

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 comparator drug are included in this trial.

6.1.3 Treatment arms/group

Eligible subjects will be randomly assigned at Baseline/Day 1 to 1 of the following 2 treatment arms in a 1:1 ratio

- Brolucizumab 6 mg: 6 x q4w followed by 48 weeks of IFT from Week 24 onwards
- Aflibercept 2 mg: 6 x q4w followed by 48 weeks of IFT from Week 24 onwards

6.1.4 Treatment duration

The planned duration of treatment is 18 months (72 weeks). Discontinuation of study treatment for a subject occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

[redacted]

Subjects who prematurely discontinue study treatment for any reason except withdrawal of consent should continue in the study and carry out the scheduled visits and assessments, at the discretion of the subject and investigator.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Prior medication, i.e. any medication taken within 90 days prior to screening, must be recorded on the appropriate Electronic Case Report Forms (eCRFs).

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate eCRFs.

Each concomitant medication must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue to take study treatment or should discontinue study treatment but still continue participation in the study.

6.2.1.1 Permitted concomitant therapy

During the study, if the fellow eye develops visual impairment due to ME secondary to CRVO or other disease, it may also be treated with standard of care at the discretion of the investigator (i.e. treatment of the fellow eye with anti-VEGF medication other than brolucizumab is allowed). Fellow eye treatment will be captured in the eCRF. The fellow eye must be monitored according to routine practice and adverse events (AEs) captured in the eCRF.

In case of development of peripheral retinal neovascularization in the study eye, it may be treated with laser according to the investigator's routine practice.

If needed, administration of topical ocular corticosteroids in the study eye is allowed during the study. Corticosteroids administered via intra-nasal, inhaled, intra-articular or non-extensive dermal route are also permitted during the study.

If cataract surgery or yttrium aluminum garnet (YAG) laser is necessary, it should be scheduled in a way not to disturb the schedule for study treatment.

6.2.2 Prohibited medication

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

Table 6-2 Prohibited medications/procedures

Medication / Procedures	Prohibition period	Action taken
Study eye		
Any periocular injection or intraocular administration of 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

[redacted]

Medication / Procedures	Prohibition period	Action taken
Laser photocoagulation (focal/grid)	Before Week 24	Continue study treatment at the investigator's discretion
Any investigational drug, biologic or device	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 (except temporary use for COVID-19 treatment)	Any time	Discontinue study treatment

In the fellow eye, treatment with investigational product (drug, biologic or device) is prohibited. Any medication used to treat the fellow eye should be recorded in the appropriate eCRF page.

6.2.3 Rescue medication

Per the investigator's discretion, the study eye may receive rescue treatment with macular laser photocoagulation (focal or grid) from Week 24 onwards if **ME** worsening results in a ≥ 10-letter loss in BCVA at 2 consecutive visits or a ≥ 15-letter loss in BCVA at 1 visit in the study eye compared to best previous measurement, and the study eye BCVA value is not better than the baseline value.

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 signs the informed consent form 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 in the electronic data capture (EDC) system.

Subjects who have been screen failures but are rescreened (see Section 8.1) will be assigned a new Subject No. if rescreening occurs beyond 14 days from the original screening date.

6.3.2 Treatment assignment, randomization

All screened subjects must be added to the Interactive Response Technology (IRT) system. At the Baseline Visit/Day 1 all eligible subjects will be randomized via IRT to 1 of the treatment arms in a ratio of 1:1. The randomization will be stratified by the following demographic groups: Japanese region, Chinese region (including Taiwan and Hong Kong) and rest of world (RoW) region.

The unmasked investigator or his/her delegate will contact the IRT after receiving confirmation from the masked investigator that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the study treatment

[redacted]

packages (each containing 1 vial) to be dispensed to the subject. The randomization number will not be communicated to subject or site users.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

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

6.4 Treatment masking

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 are no longer present.

This study will be double-masked, with subjects randomized to be treated with brolucizumab 6 mg or aflibercept 2 mg. The clinical study team will be masked to treatment assignments until Week 52 Database lock and will be unmasked once the Week 52 Database lock is reached. However, masking to the original treatment assignment will be maintained at the site level (patients, masked study site personnel, masked monitors) until the end of the study.

Unmasking of investigators and site personnel directly involved in the conduct of the study will only occur in case of subject emergencies (see Section 6.6.2), and then at the time of the final analysis (see Section 4.4), at the conclusion of the study.

In the event of a medical emergency or an adverse event (AE) during the study where the knowledge of subject treatment is required (e.g. in case of Suspected Unexpected Serious Adverse Reaction (SUSAR)), an 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 investigational product. The unmasked site personnel and unmasked injecting investigator must not perform BCVA assessments, complete ophthalmic examination, disease stability assessments or administer the National Eye Institute Visual Function Questionnaire-25 (NEI 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 of AEs for subjects during the course of the study.

[redacted]

The unmasked investigator/site personnel should, however, assess the subject's functional vision (e.g. finger counting) and may perform other safety assessments as needed immediately following injection.

After randomization, the **unmasked** investigator/site personnel **must** not change their role to perform a masked role. Only when a **masked** investigator needs to change to become an unmasked investigator, he/she may change as long as the person is not serving in the Principal Investigator role. This change must be agreed with the Sponsor. Every effort must be made to limit the number of unmasked study personnel to ensure the integrity of this masked study.

Treatment masking of individual subjects will remain intact until the database lock has occurred by ensuring that randomization data are kept strictly confidential until the time of unmasking and will not be accessible by anyone else involved in the study except the unmasked/treating investigator. During and after database lock at Week 52 and Week 76, the masked personnel at site and subjects will remain masked to the treatment assignment until the conclusion of the study.

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

[redacted]

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments are not permitted.

Deviations to the mandatory dosing intervals during the loading phase and/or dose adjustments during the whole study are not allowed. Study treatment can be interrupted if warranted due to an AE.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

IRT needs to be accessed by unmasked study personnel at every visit, even if study treatment is not needed at that visit as per the assessment of the masked investigator (see Section 6.7.2). Registration of all visits in the IRT system is necessary, and when treatment is warranted, IRT will provide a medication (kit) number to administer the assigned investigational product to the subject. No kit number will be provided in instances when the subject is intended to receive a sham injection. 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.

[redacted]

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when 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 IRT system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken. If the treatment code needs to be broken in the interest of subject safety, the investigator is encouraged to contact an appropriate Sponsor representative prior to unmasking if there is sufficient time.

It is the unmasked or masked 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
- name (if available)
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that 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 comparator drugs (Section 6.1.1). For both brolucizumab and aflibercept, the study drug packaging 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 1 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 study personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

6.7.1 Handling of study treatment

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 registered in the IRT system and stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance

[redacted]

with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

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

The unmasked 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.

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.

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 system.

There will be 2 treatment phases for IVT injections:

Loading Phase

In the loading phase, treatment with either brolucizumab (6 mg) or aflibercept (2 mg) will occur every 4 weeks for six (6) consecutive injections (baseline, Weeks 4, 8, 12, 16 and 20).

Every effort should be made to ensure that the subject adheres to the visit/treatment schedule.

Individualized Flexible Treatment (IFT) Phase

The IFT phase is defined as follows (see Figure 6-1):

- The assessment of disease stability is performed at each visit by the masked investigator as of Week 24, and is guided by the stability of visual acuity and/or anatomical parameters (e.g. subretinal fluid, intraretinal fluid, retinal thickness (CSFT)), within the previous 3 visits.
- As long as there is no disease stability, subjects will receive active injections every 4 weeks.
- When disease stability is reached, treatment is interrupted.

The IRT system will allocate active/sham injections as per the masked investigator's assessment of disease stability. A disease stability assessment will also be performed at Week 76/EOS visit, however no study treatment will be administered.

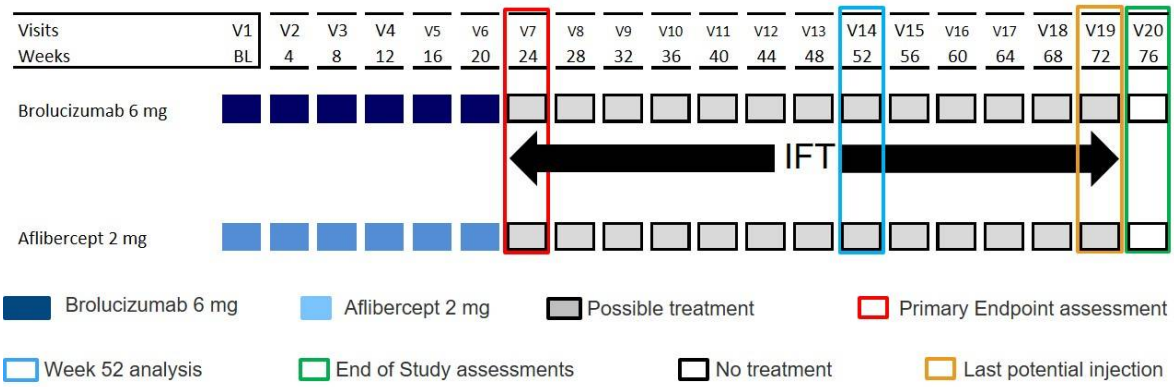
Brolucizumab or aflibercept (or sham) should be administered in the study eye on the day of the study visit or, if this is not possible, the recommendation is for this to be performed within 3 days after the occurrence of the study visit (except for Baseline/Day 1, in which case study treatment administration should occur within the next 24 hours), or no later than within the visit window as described in Section 3 and Section 8. If assessments and treatments take place on the same day, treatment must occur after completion of the efficacy assessments described in Section 8.3 and pre-injection safety measures (tonometry, slit lamp and fundus examinations)

[redacted]

described in Section 8.4.3. If study visit assessments and a corresponding treatment occur on separate days, a repeat safety check-up should be performed prior to treatment of the eye and results documented in the source documents. If any safety concern arises related to the study eye that, in the opinion of the investigator, may be further impacted by the study treatment or injection procedure, treatment needs to be cancelled. Any adverse events must be recorded in the eCRF.

The assessment of the masked/evaluating investigator will be passed to the unmasked/treating investigator or delegate in order to be entered in the IRT system and obtain the applicable treatment, active or sham, as assigned by IRT.

Figure 6-1 Dose and treatment schedule



V: Visit; BL: Baseline; IFT: Individualized Flexible Treatment

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 subjects with active ocular or periocular infections and in subjects 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.

From Week 24 to Week 72 inclusive, a sham treatment will be performed to maintain subject masking in case treatment with brolucizumab or aflibercept is not deemed necessary by the investigator. For the sham treatment the tip of an injection syringe (the hub without a needle) will be used.

[redacted]

7 Informed consent procedures

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

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

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol) and collecting any study-relevant information. 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 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, the informed consent is to be updated and then must be discussed with the subject.

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

[redacted]

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

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

[redacted]

appropriately documented and confirmed by way of standard informed consent procedures at the earliest opportunity when the subject will be back at the trial site.

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 subject's source documentation. Data must be entered as appropriate in the eCRF in a timely manner (see Section 11.1).

A planned study visit schedule will be established at Baseline/Day 1, randomization (first day of treatment), for all subjects. All post-baseline and/or subsequent scheduled visits will be calculated based on the Day 1 visit date. All efforts should be made to adhere to all scheduled visits and assessments as outlined in the assessment schedule (Table 8-1).

A ± 7 days visit window is allowed (except for Baseline/Day 1), should the subject be unable to return per scheduled visit. All efforts should be made to revert back to the planned visit schedule taking into consideration the restrictions on the minimum treatment interval for the study treatment, i.e. 2 consecutive injections should be spaced by at least 21 days.

For a given protocol visit (except for Baseline/Day 1), assessments can be performed on 2 consecutive days in which both days must occur within the ± 7 days visit window.

Treatment is intended to be administered on the day of study visit or, if this is not possible, within 3 days after the study visit at which the per-protocol assessments took place (except Baseline/Day 1, in which case study treatment administration should occur within the next 24 hours).

For all visits, efficacy assessments (Section 8.3) and safety assessments (Section 8.4) should be performed prior to any administration of study treatment and/or rescue medication.

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the End of Study 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 subject'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	Loading Phase						Individualized Flexible Treatment Phase													Follow-up
Visit Name	Screening	Baseline / Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19 / EOT	20 / EOS
Weeks	-4 to -1	1	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76
Informed Consent	X																				
[redacted]																					
Inclusion/Exclusion Criteria	X	X																			
Demography	X																				
Medical History/Current Medical Conditions	X																				
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X																				X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X							X							X						X
Clinical Chemistry	X							X							X						X
Urinalysis	X							X							X						X
Pregnancy Test (serum)	X														X						X
Pregnancy Test (urine)		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	
Visual Function Questionnaire-25 (VFQ-25)[2]		X						X							X						X
[redacted]																					
Blood Collection for Anti-Drug Antibody (ADA)[3]	X		X		X			X			X				X						X
Blood Collection for Study Drug Systemic Exposure[3]	X		X		X			X			X				X						X
Best-corrected Visual Acuity (BCVA)	X[4]	X	X	X	X	X	X	X[4]	X	X	X	X	X	X	X[4]	X	X	X	X	X	X[4]

[redacted]

Period	Screening	Loading Phase						Individualized Flexible Treatment Phase													Follow-up
Visit Name	Screening	Baseline / Day 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19 / EOT	20 / EOS
Weeks	-4 to -1	1	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76
Intraocular Pressure (IOP)	X[4]	X	X	X	X	X	X	X[4]	X	X	X	X	X	X	X[4]	X	X	X	X	X	X[4]
Ophthalmic Exam[5,8]	X[4]	X	X	X	X	X	X	X[4]	X	X	X	X	X	X	X[4]	X	X	X	X	X	X[4]
Spectral Domain Optical Coherence Tomography (SD-OCT)[8]	X[4]	X	X	X	X	X	X	X[4]	X	X	X	X	X	X	X[4]	X	X	X	X	X	X[4]
[redacted]																					
Disease Stability Assessment								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	X	X
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Administration		X	X	X	X	X	X	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	

[redacted]

[2] VFQ-25: To be collected prior to starting any assessment for that visit day
[3] Blood samples will be taken from all subjects, but ADA and systemic exposure will only be assessed for the Brolucizumab assigned subjects
[4] Both eyes at only designated visits
[5] Ophthalmic exam includes posterior segment and slit lamp examination. Pupil dilation optional according to local practice
[redacted]
[7] Study drug administration pending disease stability assessment (IFT regimen). Sham injection will be performed if no study drug administration is required
[8] Additional ophthalmic examinations and images will be performed in case of any signs of intraocular inflammation

[redacted]

8.1 Screening

A screening period of up to 4 weeks will be used to assess subject eligibility.

For the purpose of screening, fluorescein angiography (FA) images from a previous *routine* evaluation may be used as long as FA was performed within 3 days of the screening visit using Central Reading Center (CRC)-certified equipment and technician/investigator.

One-time reassessment of subjects is allowed, **except** for the purpose of capturing new BCVA assessments that previously failed to qualify the subject. 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 the subject must be reconsented and all screening procedures must be repeated. Medical judgment should be exercised to ensure that treatment of CRVO is not withheld in order for a subject to participate in the study.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and who are 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 eCRF page. The demographic information, informed consent, inclusion/exclusion and disposition eCRF 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 SAE Section 10.1.2 for reporting details). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. If the subject is not eligible to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

8.2 Subject demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

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

- Age
- Sex
- Race/Ethnicity
- Physical examination
- Vital signs
- Study eye
- Best-corrected visual acuity
- Macular edema characteristics
- Intraocular pressure

[redacted]

- Ophthalmic examinations
- Retinal imaging
- Laboratory test results
- Pregnancy test
- VFQ-25 questionnaire
- Prior/concomitant medications
- Medical history/current medical conditions
- Adverse events

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

- Best-corrected visual acuity with ETDRS-like charts at an initial testing distance of 4 meters
- [redacted]

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 in the study eye at every study visit and in both eyes at screening, Week 24, Week 52 and Week 76/EOS 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 at an initial testing distance of 4 meters. The details of the refraction technique and VA testing, as well as training material, are provided in the applicable manual. Certification of the assessment procedures and VA assessors will occur prior to any evaluation of study subjects.

8.3.2 Optical coherence tomography

Spectral Domain Optical Coherence Tomography (SD-OCT) images will be obtained and assessed in the study eye at every study visit and in both eyes at screening, Week 24, Week 52 and Week 76/EOS visit. Only SD-OCT machines can be used (e.g. no time domain OCT).

These assessments will be performed by a trained technician or investigator at the sites and should be performed **after** BCVA assessment and **prior** to any study drug administration. Masked investigators will evaluate the SD-OCT to assess the status of disease stability. The SD-OCT machine used for an individual subject should not change for the duration of the study.

[redacted]

CSFT and central foveal thickness will be measured by SD-OCT. The CSFT evaluated in this study represents the average retinal thickness of the circular area within 1 mm diameter around the foveal center.

[redacted]

A Central Reading Center (CRC) will be used in this study. The CRC will provide sites with a Study Manual and training materials for the specified study ocular images. Before any study images are obtained, site personnel, test images, systems and software will be certified and validated by the CRC as specified in the Study Manual. All SD-OCT [redacted] images will be obtained by trained and study-certified site personnel at the study sites and forwarded to the CRC for independent standardized analysis and storage.

The CRC will create a database with the agreed variables as indicated in the CRC grading charter (a separate document) and will transfer the data from this database to Novartis for analysis. The CRC data will be used for the evaluation of the objectives having SD-OCT [redacted] parameters to ensure a standardized evaluation. For further procedural details, the investigator should refer to the applicable manual provided by the Central Reading Center.

[redacted]

[redacted]

8.3.4 Appropriateness of efficacy assessments

The use of BCVA as a measure of retinal function as well as SD-OCT images to analyze anatomical changes are standard assessments in this indication and are required for a comparative evaluation of this trial with the existing evidence from previous trials.

[redacted]

8.4 Safety

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

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.

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

For details on AE collection and reporting, refer to Section 10.1.

Table 8-2 Physical Assessments

Assessment	Specification

[redacted]

Physical examination	Physical examination will be performed at Screening and at EOS visit as a general health check according to local clinical practice. Clinically relevant findings that are present prior to signing informed consent must be included in the eCRF capturing Medical History. Significant findings identified after providing written informed consent which meet the definition of an Adverse Event must be recorded on the appropriate AE eCRF page.
Vital signs	Vital signs include assessment of sitting blood pressure (systolic and diastolic pressure in mmHg) and pulse rate (beats per minute) and will be collected at all visits. In case there is an elevated blood pressure measurement as specified in the exclusion criteria, at the screening and baseline visits, the blood pressure measurement should be repeated after 20 minutes. If the repeat measurement is elevated, then the subject 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.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected at screening, Week 24, Week 52 and Week 76/EOS visit. 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.

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.

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

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or adverse event as appropriate.

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	• Serum clinical chemistry tests: Serum electrolytes (sodium, potassium, chloride, phosphorus, calcium, magnesium), uric acid, urea nitrogen, creatinine, albumin, glucose, total protein, total bilirubin and direct bilirubin, serum glutamic oxaloacetic transaminase (SGOT)/ aspartate aminotransferase (AST), serum glutamic pyruvic transaminase (SGPT)/ alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) • Additional clinical chemistry tests: Lipids panel - triyglycerides (TG), low-density lipoproteins (LDL), high-density lipoproteins (HDL), total cholesterol (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

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

[redacted]

Highly effective contraception is required for women of child-bearing potential during the study drug administration and for 3 months after stopping the investigational medication.

A **serum** pregnancy test will be conducted for all women of child-bearing potential to assess pregnancy before inclusion into the study at Screening visit and then at Week 52 and Week 76/EOS visit. During the study, monthly **urine** pregnancy testing will be performed at visits when serum pregnancy testing will not be conducted. Results of all pregnancy testing must be available as source documentation.

Assessment of fertility

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.

8.4.3 Ophthalmic examination

The ophthalmic exam will consist of the following:

- **Intraocular pressure** (IOP) will be assessed in the study eye, pre-dose and post-dose at every scheduled visit. The method used for measuring a subject's IOP must remain consistent throughout the study. In the fellow eye, IOP will be assessed at screening, Week 24, Week 52 and Week 76/EOS visit. The values recorded in mmHg for either eye will be entered into the eCRF.

  Post-dose IOP should be assessed within 60 minutes after every IVT/sham injection and, if ≥ 25 mmHg, assessment should be repeated until back to normal. Treatment and close monitoring of an elevated IOP should be performed by the investigator according to local clinical practice.
- **Anterior 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 at screening, Week 24, Week 52 and Week 76/EOS visit and at the discretion of the investigator). The results of the examination of either eye must 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 of 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.
- **Posterior segment (indirect fundus) examination** will be conducted by the investigator at the screening visit for both eyes. An examination of the peripheral retina must also be

[redacted]

conducted to ensure that the intravitreal injection can be safely performed. As of baseline visit, the posterior segment examination will be performed at every visit in the study eye (fellow eye will be examined at Week 24, Week 52 and Week 76/EOS visit and at the discretion of the investigator). The results of the examination of either eye must be recorded in the source documents.

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 the 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.

Pupil dilation for slit lamp and posterior segment examination is optional according to local practice.

Clinically significant abnormal findings (as judged by the masked investigator) from slit lamp or posterior segment examination should be recorded as an AE in the eCRF.

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 wide-field or with peripheral sweeps). These additional assessments will be documented in the source and appropriate eCRF pages as applicable. The images are requested to be uploaded onto the CRC portal.

8.4.4 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

8.5.1.1 Patient Reported Outcomes (PRO)

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

[redacted]

degeneration (AMD). 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 patients with DME (Klein et al 2001) and RVO (Varma et al 2012).

The NEI VFQ-25 will be administered to subjects at sites where validated local language versions are available and where they are approved by the corresponding IRB/IEC. At baseline and Weeks 24, 52 and 76 (EOS), the questionnaire should be administered to subjects **before** completing any other study procedures of the visit. Answers to NEI VFQ-25 will be captured electronically independently from the eCRF (in a dedicated database). The subject's answers to the interview questions will be reviewed by masked site staff.

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

Completed questionnaires will be reviewed and assessed by the masked/evaluating investigator for responses that may indicate potential AEs or SAEs before completion of the study visit. If AEs or SAEs are confirmed, the evaluating investigator should not encourage the subject to change responses reported in the completed questionnaires.

Evaluating investigators should follow reporting instructions outlined in Section 10 of the protocol.

8.5.2 Imaging

Refer to Section 8.3.2 Optical coherence tomography [redacted].

8.5.3 Anti-drug antibodies (immunogenicity)

Anti-drug antibodies (ADA) levels will be assessed from subjects assigned to brolucizumab treatment **only**. However, in order to maintain masking, collection of blood samples for ADA assessment will be performed in **both** treatment arms (brolucizumab and aflibercept) at screening, Weeks 4, 12, 24, 36, 52 and 76 (EOS).

Samples collected from subjects assigned to aflibercept treatment will **not** be assayed for ADA nor for systemic exposure. Systemic exposure of brolucizumab will be measured concomitantly with ADA levels for interpretation purposes. No pharmacokinetic parameters will be determined from brolucizumab systemic exposure.

Additional pharmacodynamic assessment may be conducted on the samples wherever permitted by local regulation.

Blood draws should take place **prior** to the injection/sham procedures. A standardized procedure for the collection, numbering, processing, storage and shipment of these blood samples is provided by the central laboratory and details can be found in the central laboratory manual.

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

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

A subject will be considered to have completed the study when the subject 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 subjects 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:

- Subject/guardian decision
- Pregnancy (see Section 8.4.2 and Section 10.1.4)
- Use of prohibited treatment (see Section 6.2.2)
- Any situation in which continuation with study treatment might result in a safety risk to the subject
- Following emergency unmasking (see Section 6.6.2)

If premature discontinuation of study treatment occurs, the following should be done as appropriate:

[redacted]

- The investigator must contact the IRT to register the subject's discontinuation from study treatment.
- The investigator should make a reasonable effort to understand and document the primary reason for the subject's premature discontinuation of study treatment using the appropriate eCRF page.
- Subjects who prematurely discontinue study treatment for any reason, except for withdrawal of consent (refer to Section 9.1.2), should continue in the study with all the scheduled visits and assessments (except disease stability assessment, administration of study treatment, post-injection assessment and adherence to prohibited medication list) until EOS, at the discretion of the investigator or the subject.
- Subjects who decide not to participate in the study further should NOT be considered withdrawn from the study, UNLESS they withdraw their consent (see Section 9.1.2). **Where possible, subjects should return for the EOS visit assessments to be performed as scheduled** in Table 8-1.
- If a subject fails to return 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 (see Section 9.1.3).
- If the subject cannot or is unwilling to return at 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 premature study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:
  - New/concomitant treatments
  - Adverse events/Serious Adverse Events

In the event that premature study treatment discontinuation occurs because treatment code has been broken, please refer to Section 6.6.2.

9.1.1.1 Replacement policy

Subjects who started treatment but prematurely discontinued treatment and/or study will not be replaced.

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data.

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.

[redacted]

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.

The investigator must contact the IRT to register the subject's withdrawal of consent.

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 collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

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

For EU and RoW: 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 may include:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendation from the Data Monitoring Committee (DMC) after review of safety and efficacy data
- Discontinuation of study drug development
- Practical reasons, including slow enrollment
- Regulatory or medical reasons

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.

[redacted]

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.

After study completion the subject might receive standard of care if needed.

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.

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 may also 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 eCRF under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. the severity grade
   mild: usually transient in nature and generally not interfering with normal activities
   moderate: sufficiently discomforting to interfere with normal activities
   severe: prevents normal activities
2. its relationship to the study treatment or the ocular injection procedure. 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 treatment arms, 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

[redacted]

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 with the study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - no action taken (e.g. further observation only)
   - (investigational) treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - subject hospitalized/subject's hospitalization prolonged (see Section 10.1.2 for definition of SAE)
6. its outcome
   - not recovered/not resolved;
   - recovered/resolved;
   - recovered/resolved with sequelae;
   - fatal; or unknown.

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

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

Adverse event monitoring should be continued until 30 days after 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 are included in Section 16.1.

[redacted]

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
    - 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.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

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

[redacted]

Novartis Safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office & Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an 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.

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 (female participants only).

The pregnancy (for female participants) should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis CMO & PS Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to brolucizumab (investigational) and/or aflibercept, with any pregnancy outcome.

Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record in the eCRF and in the Dispensing Log at the study site, irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE.

[redacted]

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 date and time of injection)	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 (Section 10.1.1, Section 10.1.2, and Section 10.1.3).

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 the clinical trial and, based on the safety data and critical efficacy variables recommend to the sponsor whether to continue, modify or terminate the 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.

10.2.2 Adjudication Committee

Not required.

11 Data Collection and Database management

11.1 Data collection

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

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 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

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

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

[redacted]

eSource

eSource is a data collection system allowing electronic capture of source data and study data, as required per protocol. eSource is intended to be used for this study. eSource replaces the need for using an eCRF. If it is not possible to use eSource for source data capture due to exceptional circumstances, data capture and data management will revert to paper and other electronic methods as appropriate.

This study will incorporate electronic technology (eSource Direct Data Entry (DDE)) to capture source documents and source data electronically, consistent with final (Center for Drug Evaluation and Research (CDER) 2013) FDA guidance regarding electronic source and regulations related to the maintenance of adequate subject case histories (21 CFR 312.62 [b]). All electronic source documentation and data collected in this study will "meet the same fundamental elements of data quality (e.g. attributable, legible, contemporaneous, original, and accurate) that are expected of paper records" into a system that is fully validated and conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the system(s) until they have been appropriately trained.

Study sites using eSource DDE will be supplied with a tablet personal computer to directly record subject data and clinical observations on electronic forms with a similar look, feel, and behavior to paper forms. The system will permit the collection of both structured and unstructured information including ad-hoc comments, drawings, and relevant clinical notes the investigative site deems important. Information to be originally captured and reviewed electronically shall include details of the subject visit and the protocol required assessments performed as a part of these visits, medical history, and concomitant medications.

Certain data may be captured via other source documentation (such as safety laboratory data report, imaging) and then transcribed, uploaded or transferred into the eSource DDE system. This, and any additional data treated in this manner, will be source data verified by the study field monitor per the monitoring plan and the location of source data (i.e. source, paper or a local electronic system) will be documented prior to study start. The eSource system has the ability to illustrate when a document has been entered from another source. When using an electronic source record as the original point of data capture, there is no additional data entry step for the site for data collected directly into the application. Rather, the electronic source record directly populates the study database.

Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the vendor working on behalf of Novartis.

Remote monitoring of the original electronic source records will take place, however on-site monitoring inspections will continue to take place in order to review data entry of source documentation directly captured on paper and transcribed into the system, to ensure protocol adherence, to assess site operational capabilities, and to perform other monitoring activities that cannot be performed remotely.

The investigator must certify that the data entered into eSource are complete and accurate.

11.2 Database management and quality control

Novartis personnel will review the data entered by investigative 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 investigative 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. VFQ-25 data will be processed centrally by a designated vendor 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.

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

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

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

[redacted]

11.3 Site monitoring

Before study initiation, at a site initiation visit and/or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE or

[redacted]

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 Clinical Research Associates (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 (OCT, CP, FA, wide-field imaging), and the results of any other tests or assessments. All information on eCRFs 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 eCRFs 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 database including all Week 52 data will be locked once all subjects have completed the Week 52 visit or terminated the study prior to Week 52. Data for the primary endpoint, change from baseline in BCVA at Week 24, will be derived from this database. All subjects still in the study beyond Week 52 will continue to receive masked treatment as scheduled through the planned study duration of 76 weeks. The analysis of the data collected after the Week 52 visit will be performed once all subjects complete the EOS visit or discontinue from the study.

Summary statistics will be presented by treatment group unless otherwise specified. For continuous variables, summary statistics will generally include: n, mean, standard deviation, median, quartiles, minimum, and maximum. For categorical variables, these will generally include: n, frequency and percentage in each category. Further technical details and discussions of the statistical considerations will be provided in the SAP.

Additional analyses may also be conducted to evaluate the impact of the COVID-19 pandemic.

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

[redacted]

12.1 Analysis sets

The All-Enrolled Analysis Set includes all subjects who have signed informed consent and are assigned subject numbers.

The Randomized Analysis Set (RAS) consists of all enrolled subjects who are randomized in IRT. Subjects are considered randomized when they have been deemed eligible for randomization by the investigator and given a randomization number. Subjects will be analyzed according to the treatment assigned to them at randomization.

The Full Analysis Set (FAS) comprises all randomized subjects who receive at least 1 IVT injection of the study treatment. Subjects in the FAS will be analyzed according to the treatment assigned to them at randomization.

The Safety Analysis Set (SAF) includes all subjects who receive at least 1 IVT injection of the study treatment. Subjects in the Safety Set will be analyzed according to the study treatment from which they received the majority of treatments up to and including Week 52.

The Per Protocol Set (PPS) is a subset of the FAS and will exclude or censor data from subjects with protocol deviations (PDs) and analysis restrictions (ARs) that are expected to majorly affect the validity of the assessment of efficacy at Week 24 and/or Week 52 including, for e.g. lack of compliance (including missed treatments and treatment misallocation), missing data, prohibited concomitant medication, and deviations from inclusion/exclusion criteria. Confounded data or discontinuation from study treatment due to lack of efficacy and/or safety do not constitute, in itself, a reason for exclusion from the PPS.

Before the Week 52 database lock the relevant protocol deviations and analysis restrictions will be identified at the subject level in the 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 (refer to Table 12-1) using PPS, i.e. similar conclusions on non-inferiority based on both estimands are expected. Inconsistencies in the results will be examined and discussed in the Clinical Study Report.

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. Summary statistics for other analysis sets will only be generated if these are anticipated to be different given the subset of the subjects included in the particular analysis set. Relevant medical history and current medical conditions will be tabulated by system organ class (SOC) and preferred term 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 summary statistics for exposure to study treatment will be provided for the SAF, FAS and PPS populations. For the efficacy analysis sets (FAS and PPS), the cumulative number of active and sham IVT injections will be presented by visit for the period baseline to Week 52/Week 72, including a separate analysis for the loading phases, i.e. up to Week 20 (6 x q4w loading), and maintenance phase (Week 24 to Week 52/Week 72). For the SAF, the summary will include exposure data up to Week 52/Week 72.

Prior medication and concomitant therapies

The number and percentage of subjects taking prior medication (any medication taken up to 90 days prior to screening) or concomitant therapies will be summarized by preferred term according to the WHO Drug Reference List dictionary using the SAF and FAS (in case there are differences between the two populations). 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. Further details will be provided in the SAP.

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 24. BCVA will be assessed by the masked investigator using ETDRS-like charts at an initial distance of 4 meters.

The primary analysis of the primary endpoint will be based on the FAS.

12.4.2 Statistical model, hypothesis, and method of analysis

The objective related to the primary endpoint is to demonstrate non-inferiority of brolucizumab versus aflibercept with respect to change from baseline in BCVA at Week 24, assuming a non-inferiority margin of 4 ETDRS letters.

Let:

B = Brolucizumab 6 mg - 6 x q4w loading

A = Aflibercept 2 mg - 6 x q4w loading

Consider the following non-inferiority hypotheses related to a non-inferiority margin of 4 letters:

H_0: $\mu_B - \mu_A \leq$ -4 letters versus H_A: $\mu_B - \mu_A >$ -4 letters

where μ_B and μ_A are the corresponding unknown true mean changes from baseline in BCVA at Week 24 in the brolucizumab and aflibercept arms, respectively.

The primary estimand associated with the above hypothesis is defined as the between-treatment difference in change from baseline in BCVA at Week 24, excluding the effect of relevant CRVO prohibited/alternative medication(s) applied to the study eye (e.g. alternative anti-VEGF treatments for CRVO, laser, intraocular corticosteroids, among others as further detailed in Section 6.2.2 and in the SAP). The analysis set for the primary estimand will be the FAS.

Based on the FAS, the above hypotheses will be tested via an analysis of variance (ANOVA) model. The model will include treatment, baseline BCVA ($\leq$ 34, 34 - 55, $\geq$ 55 letters) and age

[redacted]

category (< 65, ≥ 65) as factors. Additional factors, e.g. ethnicity, may also be included as appropriate, as well as interactions between treatment and factors of interest.

The two-sided 95% confidence interval (CI) for the least square mean difference (brolucizumab - aflibercept) at Week 24 will be presented. Non-inferiority will be considered established if the lower limit of the corresponding 95% CI is greater than -4 letters. The same approach for non-inferiority assessment in change from baseline in BCVA at Week 24 will be applied to any supplementary estimand.

The primary estimand and supplementary estimand of interest are noted in Table 12-1 below together with their key attributes. Sensitivity to the primary estimand will only be explored if the proportion of subjects with missing or censored data is deemed large enough so as to potentially impact the results from the analyses. The estimands outlined below will be discussed in further detail in the SAP.

Table 12-1 Primary and supplementary estimands

			Use of data after discontinuation of study treatment due to[1]:		
Estimand	**Estimand definition**	**Analysis set**	**lack of efficacy or safety**	**any other reason**	**Statistical methods (Including missing data strategy)**
Primary estimand	Difference in change from baseline in BCVA at Week 24 excluding the effect of CRVO prohibited/ alternative medication(s)	All randomized subjects who receive at least 1 IVT injection of the randomized study treatment (FAS)	Included	Included	Analysis of variance (ANOVA) model assessed at a one-sided significance level of 0.025, and including terms for treatment, baseline BCVA (≤ 34, 34 - 55, ≥ 55 letters) and age category (< 65, ≥ 65), and using LOCF imputation for missing/censored data.
Sensitivity to primary estimand	Difference in change from baseline in BCVA at Week 24 excluding the effect of CRVO prohibited/ alternative medication(s)	All randomized subjects who receive at least 1 IVT injection of the randomized study treatment (FAS)	Included	Included	MMRM[2] approach based on observed data (assuming data missing at random), and including fixed effect terms for treatment, visit, visit by treatment interaction, baseline BCVA (≤ 34, 34 - 55, ≥ 55 letters) and age category (< 65, ≥ 65)

Estimand	Estimand definition	Analysis set	Use of data after discontinuation of study treatment due to[1]: lack of efficacy or safety	Use of data after discontinuation of study treatment due to[1]: any other reason	Statistical methods (Including missing data strategy)
Supplementary estimand	Difference in change from baseline in BCVA at Week 24 excluding the effect of CRVO prohibited/ alternative medication(s) and protocol deviations as per the definition of the PPS	All randomized subjects who adhere to the protocol as per the definition of PPS	Included	Not included; treated as missing	ANOVA model as per the primary estimand LOCF imputation for missing/censored data

[1]Note that, for all estimands as applicable, all data captured until the start of prohibited medication or alternative medication for ME secondary to RVO after discontinuation from study treatment will be included in the analysis.
[2]MMRM: Mixed Model Repeated Measures

12.4.3 Handling of missing values/censoring/discontinuations

As stated in the definition of the primary estimand, missing BCVA values will be imputed by Last Observation Carried Forward (LOCF) as the primary approach. For subjects with no post-baseline BCVA value, the baseline value will be carried forward. Data collected after the start of alternative CRVO treatments in the study eye (e.g. other anti-VEGF treatment, certain laser procedures or intraocular corticosteroids; further details will be discussed in the SAP) will be censored.

The LOCF approach is expected to be sensitive to an early study treatment termination/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 as described above (CRVO), 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 an early study termination during the loading phase, the LOCF method will result in a conservative estimate, potentially underestimating the true outcome.

LOCF is an established method within the assessment of efficacy of anti-VEGF treatments in terms of BCVA outcome. It is important to note that, in order to facilitate a meaningful treatment effect assessment, 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. In the aflibercept Phase III studies COPERNICUS and GALILEO (CRVO) and VIBRANT (BRVO) missing BCVA data was imputed based on LOCF.

12.4.4 Sensitivity and supplementary analyses

Sensitivity and supplementary analyses for the primary endpoint, change from baseline in BCVA at Week 24, are specified in terms of sensitivity and supplementary estimands as described in Table 12-1. This describes different approaches to deal with intercurrent events such as intake of CRVO prohibited/alternative medication in the study eye, or any event leading to exclusion from the PPS, and the resulting missing/censored data. The same approaches to deal with intercurrent events and/or missing data may be applied to some or all of the secondary endpoints as appropriate. For the primary and relevant secondary endpoints, descriptive analyses based on observed data only (with and without censoring of data collected after use of relevant prohibited/alternative medication for CRVO as described in Section 6.2.2 and further detailed in the SAP) may also be produced.

The following subgroup analyses will be explored using the FAS and the statistical model described in the primary estimand in Table 12-1:

- Age category (< 65, ≥ 65 years)
- Sex (male, female)
- Baseline BCVA categories (≤ 34, 34 - 55, ≥ 55 letters)
- Duration of ME (≤ 3, > 3 months)
- Baseline CSFT (< 450, 450 - 650, ≥ 650 µm)
- Baseline status of IRF (presence, absence)
- Baseline status of SRF (presence, absence)
- Region
  - Japanese
  - Chinese
  - Rest of World

Further description of the supplementary and sensitivity analyses will be detailed in the SAP.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Secondary efficacy endpoints based on BCVA:

- Change from baseline in BCVA averaged over the period Week 40 to Week 52
- Change from baseline in BCVA averaged over the period Week 64 to Week 76
- Change from baseline in BCVA by visit up to Week 76
- Proportion of study eyes with a gain ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline
- Proportion of study eyes with a loss ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline

[redacted]

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

Secondary efficacy endpoints related to anatomy:

- Change from baseline in central subfield thickness (CSFT) averaged over the period Week 40 to Week 52
- Change from baseline in CSFT averaged over the period Week 64 to Week 76
- Change from baseline in CSFT, by visit up to Week 76
- Proportion of study eyes with presence of retinal fluid (intra- and/or subretinal fluid) by visit up to Week 76 (derived from SD-OCT, from central reading center)
- Proportion of study eyes with a CSFT < 300 µm (derived from SD-OCT, from central reading center) by visit up to Week 76

Secondary efficacy endpoints related to treatment frequency:

- Number of injections between Week 24 and Week 52
- Number of injections between Week 24 and Week 76
- Time to first re-treatment between Week 24 and Week 76

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 analysis set, SAF.

Adverse events

The number (and percentage) of subjects with treatment-emergent adverse events (events started after the first dose of study medication or events present prior to start of double-masked treatment but which increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term
- by treatment, primary system organ class, preferred term and maximum severity
- by treatment, Standardized MedDRA Query (SMQ) and preferred term

Separate summaries will be provided for study treatment related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation of study treatment or the study. In addition, a separate summary for death including on-treatment and post-treatment deaths will be provided. Separate presentations will be provided related to ocular

[redacted]

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).

Subject listings of all adverse events will be provided. Deaths and other serious or clinically significant non-fatal adverse events will be listed separately. A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

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

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

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.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit and, if ranges are available, abnormalities will be flagged with thresholds representing clinical relevant abnormality. Summary statistics of absolute and change from baseline data will be provided by treatment and visit. Shift tables using the low/normal/high classification will be used to compare baseline to the worst on-treatment value.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit, and abnormalities will be flagged (using extended normal ranges as provided by the central laboratory) with thresholds representing clinical relevant abnormality. Summary statistics of absolute and change from baseline data will be provided by treatment and visit. Shift tables using the low/normal/high classification will be used to compare baseline to the worst on-treatment value.

[redacted]

[redacted]

12.5.4 Patient reported outcomes

The VFQ-25 questionnaires will be scored at baseline and Week 24, 52 and 76 visits. Absolute and changes from baseline in VFQ-25 scores 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 antibody

Collection of blood for ADA assessment will be done at screening, Week 4, 12, 24, 36, 52 and 76 visits prior to the injection/sham, and exit/premature discontinuation. Systemic exposure of brolucizumab will be measured concomitantly with ADA levels for interpretation purposes, no pharmacokinetic parameters will be determined from brolucizumab systemic exposure.

[redacted] Subject listings of all ADA titer values will be presented for all subjects.

[redacted]

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

A sample size of 340 subjects per arm will allow assessment of non-inferiority (using a non-inferiority margin, NIM, of 4 ETDRS letters) of brolucizumab 6 mg versus aflibercept 2 mg

[redacted]

with respect to the change from baseline in BCVA at Week 24. Assuming equal means and a common standard deviation of 14 letters, for a NIM of 4 letters and a one-sided alpha level of 0.025, there is 96% power to reject the null hypothesis that brolucizumab 6 mg is inferior to aflibercept 2 mg.

To account for a drop-out rate of 10%, a total of approximately 750 (375 per arm) subjects 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 and as required in EudraCT. In addition, upon 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 (e.g. Clinicaltrials.gov, EudraCT, etc.).

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values

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
Clinical Chemistry/ Calcium	alert	All	mg/dL	6.1	12.9	mmol/L	1.52	3.22	-
Clinical Chemistry/ Creatinine	reference	All	mg/dL	0.7	1.4	µmol/L	62	124	-
Clinical Chemistry/ Glucose (non fasting)	alert	All	mg/dL	40	450	mmol/L	2.22	24.98	-
Clinical Chemistry/ Potassium	alert	All	mEq/L	2.8	6.3	mmol/L	2.8	6.3	-
Clinical 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	-