NOVARTIS

Novartis Research and Development

RTH258

Clinical Trial Protocol CRTH258A2308 / NCT03930641

An Open-Label, Single-Arm, Multicenter, Phase IIIb Study in Patients With Neovascular Age-Related Macular Degeneration to Evaluate the Safety of Brolucizumab 6 mg in Prefilled Syringe

Document type:	Amended Protocol Version
EUDRACT number:	NA
Version number:	01 (Clean)
Clinical Trial Phase:	IIIb
Release date:	11-Apr-2019

Property of Novartis
Confidential
May not be used, divulged, published, or otherwise disclosed
without the consent of Novartis
Clinical Trial Protocol Template version 1.0 dated 01-Dec-2017

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

List of tables

List of figures

[redacted]

List of abbreviations

AE	adverse event
AMD	age related macular degeneration
Anti-VEGF	anti-vascular endothelial growth factor
ATC	Anatomical Therapeutic Chemical
CFR	Code of Federal Regulation
CMO&PS	chief medical officer & patient safety
CNV	choroidal neovascularization
CRA	clinical research associate
CRO	Contract Research Organization
DDE	direct data entry
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	investigator brochure
ICH	International Council for Harmonization of Technical Requirements for Registration for Pharmaceuticals for Human Use
IEC	independent ethics committee
IFU	instruction for use
IN	investigator notification
IOP	intraocular pressure
IRB	institutional review board
IUD	intra-uterine device
IUS	intra-uterine system
IVT	intravitreal injection
MedDRA	Medical dictionary for regulatory activities
nAMD	neovascular age related macular degeneration
PFS	prefilled syringe
QMS	quality management system
RPE	retinal pigment epithelium
SAE	serious adverse event
ScFv	single-chain fragment variable
SD card	secure digital card
SMQ	standardized MedDRA query
SUSAR	Suspected Unexpected Serious Adverse Reactions
USA	United States of America
VEGF	vascular endothelial growth factor
WHO	World Health Organization
WOCBP	women of child bearing potential

[redacted]

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy).
Assessment	A procedure used to generate data required by the study
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Investigational Drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "test substance"
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Observational Study Participant	Qualified ophthalmologist and assistants who may perform the preparation steps, to prepare and administer the PFS injection and to follow the IFU.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Screen Failure	A subject who is screened but is not treated or randomized
Source Data	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study treatment	Any drug (or combination of drugs) administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or non-investigational medicinal product(s)
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A 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.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.

[redacted]

Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 1

Amendment rationale

Based on Food and Drug Administration (FDA) feedback there was a need to change the sample size from the initially planned 10 subjects to 30. In addition, the exclusion criterion regarding prior intravitreal treatment was clarified, taking into account that available clinical evidence suggests that most of the subjects with neovascular age-related macular degeneration (nAMD) may need more frequent anti-vascular endothelial growth factor (anti-VEGF) injections, compared to other intravitreal treatments options. In addition, minor changes were made to the protocol language to provide clarity.

Changes to the protocol

5: population - page 14:

Change from:

The study population will be male and female subjects ≥ 50 years old who are diagnosed with nAMD. A minimum of 10 subjects are expected to be injected at approximately 3 sites in the United States of America.

Change to:

The study population will be male and female subjects ≥ 50 years old who are diagnosed with nAMD. Approximately 30 subjects are expected to be injected in approximately 3 sites at the United States of America.

5.1 Inclusion Criteria:

Add: definition of study population into sequence numbering; Inclusion # 3: Subjects ≥ 50 years of age at Baseline.

5.2 Exclusion Criteria:

Change Exclusion # 5 from:

Treatment with any intravitreal injection in the study eye within the past three months prior to enrollment. (Study eye is the eye eligible for intravitreal injection. If both eyes are eligible, one eye should be selected for injection at the discretion of the Investigator and according to clinical practice).

Change (split) to:

Treatment with anti-VEGF intravitreal injection in the study eye within one month prior to enrollment. (Study eye is the eye eligible for intravitreal injection. If both eyes are eligible, one eye should be selected for injection at the discretion of the Investigator and according to clinical practice).

Use of intraocular corticosteroids in the study eye during the 3-month period prior to enrollment.

These changes to the protocol are also reflected in the Summary on page 11 and 12.

[redacted]

IRB Section

Institutional Review Board (IRB) approval for this protocol amendment will be requested and needs to be received prior to implementation of the amendment at the sites.

[redacted]

Protocol summary

Protocol number	RTH258A2308
Full Title	An Open-Label, Single-Arm, Multicenter, Phase IIIb Study in Patients With Neovascular Age-Related Macular Degeneration to Evaluate the Safety of Brolucizumab 6 mg in Prefilled Syringe
Brief title	Study of the Safety of brolucizumab 6 mg in Prefilled Syringe in Patients with neovascular age related macular degeneration
Sponsor and Clinical Phase	Novartis Phase IIIb
Investigation Type	Drug
Study type	Interventional
Purpose and rationale	This is a multicenter, open label study that is designed to evaluate the safety of brolucizumab 6 mg in a prefilled syringe in subjects with neovascular age related macular degeneration and to support collection of observations of the prefilled syringe use for intravitreal injection. The use of the prefilled syringe will be observed by evaluating the ability of observational study participants, including qualified ophthalmologists and assistants who may perform the preparation steps, and to administer brolucizumab 6 mg in prefilled syringe via intravitreal injections to subjects and to follow the instructions for use.
Primary Objective(s)	To evaluate the safety of brolucizumab 6 mg delivered in prefilled syringe in subjects with neovascular age related macular degeneration
Study Design	This is an open-label, single-arm, multicenter, phase IIIb study in subjects with neovascular age related macular degeneration The Screening and Baseline Visit may be combined in one visit with one follow up visit after 7 days ± 2. Each enrolled subject will receive one injection of brolucizumab 6 mg in a prefilled syringe.
Population	Approximately 30 subjects (males and females of at least 50 years of age) diagnosed with neovascular age related macular degeneration will be enrolled in the study in approximately 3 sites in the United States of America.
Key Inclusion criteria	1. Written informed consent must be obtained before any assessment is performed. 2. Study eye is diagnosed with neovascular age related macular degeneration and deemed to be indicated for intravitreal injection at the discretion of the retina specialist. 3. Subjects ≥ 50 years of age at Baseline.
Key Exclusion criteria	1. Any active intraocular or periocular or systemic infection or active intraocular inflammation in either eye at Baseline. 2. Uncontrolled glaucoma in the study eye 3. Participants legally blind in one or both eyes. 4. History of a medical, ocular or non-ocular conditions, that in the judgment of the Investigator, would preclude a safe administration of investigational product. 5. Treatment with anti-VEGF intravitreal injection in the study eye within one month prior to enrollment.

[redacted]

	6. Use of intraocular corticosteroids in the study eye during the 3-month period prior to enrollment. 7. Any invasive intraocular surgery, prior long-acting therapeutic agent, or ocular drug release device implantation (approved or investigational) in the study eye any time during the past 3 months. 8. Receipt of any systemic anti-vascular endothelial growth factor within the last 6 months prior to enrollment. 9. Uncontrolled hypertension.
Study treatment	Brolucizumab 6 mg in a prefilled syringe.
Key safety assessments	Incidence of ocular and non-ocular AEs are considered primary endpoints.
Other assessments	Observation of the preparation and the injection using the prefilled syringe.
Data analysis	All safety analyses will be performed using the full analysis set.
Key words	Open label study, neovascular age related macular degeneration, intravitreal injection, brolucizumab prefilled syringe, observation.

[redacted]

1 Introduction

1.1 Background

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

AMD is classified into 2 clinical subtypes: the non-neovascular (geographic atrophy) or dry form and the neovascular (exudative) or wet form (Ferris et al 1984, Lim et al 2012, Miller 2013). Neovascular AMD (nAMD) is characterized by the growth of abnormal new blood vessels (neovascularization) under the retinal pigment epithelium (RPE) or subretinal space from the subjacent choroid, termed choroidal neovascularization (CNV) (Ferris et al 1984). These newly formed vessels have an increased likelihood to leak blood and serum, damaging the retina by stimulating inflammation and scar tissue formation. This damage to the retina results in progressive, severe, and irreversible vision loss

(Shah and Del Priore 2007, Shah and Del Priore 2009). Without treatment, most affected eyes will have poor central vision (20/200) within 12 months (Blinder et al 2003). Although the neovascular form of the disease is only present in about 10% of all AMD cases, it accounted for approximately 90% of the severe vision loss from AMD prior to the introduction of anti-vascular endothelial growth factor (anti-VEGF) treatments (Ferris 1983, Sommer et al 1991, Wong et al 2008, Spilsbury et al 2000, Bloch et al 2012, Campbell et al 2012).

Brolucizumab (RTH258, formerly ESBA1008) is a humanized single-chain (scFv) antibody fragment inhibitor of vascular endothelial growth factor with a molecular weight of ~26 kDa. Brolucizumab is an inhibitor of vascular endothelial growth factor - A (VEGF-A) and works by binding to the receptor binding site of the VEGF-A molecule, thereby preventing the interaction of VEGF-A with its receptors VEGFR1 and VEGFR2 on the surface of endothelial cells.

The safety and efficacy of brolucizumab 6 mg in subjects with nAMD was evaluated in two pivotal studies (CRTH258A2301 [HAWK] and CRTH258A2302 [HARRIER]), with the primary objective of noninferiority in best corrected visual acuity of brolucizumab compared to aflibercept. Brolucizumab was demonstrated to be safe and well tolerated with an ocular and systemic safety profile similar to aflibercept and non-inferior efficacy as compared to aflibercept.

In these studies brolucizumab 6 mg was administered as an injection into the eye, and was available in a vial from which medication needed to be withdrawn using a standard syringe with a filter needle. The filter needle was then replaced by a smaller gauge needle for the intravitreal injection. Prefilled syringe eliminates the need for withdrawing medication from a vial and changing needles prior to use.

The Food and Drug Administration (FDA) recommended to evaluate the ability of intended users (qualified ophthalmologists and their assistants who may perform the preparation steps) the use of brolucizumab 6 mg prefilled syringe (PFS) formulation by following the Instructions for Use (IFU) in a certain number of subjects.

[redacted]

Therefore**,** the current study will be performed for safety purposes and will support a sub-study type for collection of observations on PFS use for intravitreal injection. There will be two separate protocols as follows:

- **Current clinical protocol** is designed to collect safety data obtained from the IVT injections conducted with the use of the PFS.
- **The observational study protocol** (provided separately, [redacted] is designed to evaluate the ability of observational study participants, including qualified ophthalmologists and assistants who may perform the preparation steps, to prepare and administer to subjects IVT injection using brolucizumab 6 mg PFS and to follow the IFU.

1.2 Purpose

This is a multicenter, open label study designed to evaluate the safety of brolucizumab 6 mg PFS in subjects with nAMD. This protocol describes the collection of safety data resulting from the use of brolucizumab 6 mg PFS.

Based on this study, a separate sub-study type protocol will collect observations of PFS use for intravitreal injection (IVT). The use of PFS will be observed by evaluating the ability of observational study participants, including qualified ophthalmologists and assistants who may perform the preparation steps, to prepare and administer to subjects an IVT injection using brolucizumab 6 mg PFS and to follow the IFU. These observations and evaluations will be performed according to observational study protocol [redacted]. The results will be described in a separate report.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the safety of brolucizumab 6 mg delivered in PFS in subjects with nAMD.	• Incidence of ocular and non-ocular Adverse Events (AEs).

3 Study design

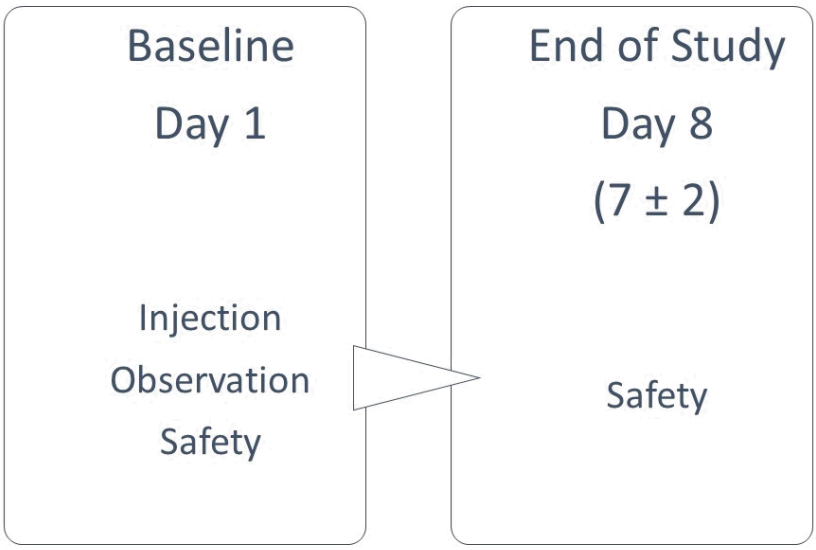
This study is an open-label, single arm, multicenter, phase IIIb study. Screening and Baseline visits may be performed on the same day. The Follow-up, which is End of Study is 7 days ± 2 days after Baseline.

Subjects who consent will undergo all screening activities to evaluate their eligibility based on the Inclusion and Exclusion Criteria. Subjects who meet all criteria will receive:

- Brolucizumab 6 mg in PFS, one injection.

[redacted]

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

This study is to evaluate the safety of the drug product in PFS where in addition under a separate observational protocol, the ability to follow the IFU and giving the brolucizumab injection in PFS to subjects with nAMD is observed.

4.2 Rationale for dose/regimen and duration of treatment

Each subject who enters the study will be given one injection of brolucizumab 6 mg in PFS. Previously performed studies in this indication suggest that brolucizumab 6 mg dose is effective and safe. One injection will be given in order to support the observation of the successful use of the device (PFS). After this injection, the follow up visit at Day 8 will be performed and there will be a safety follow-up phone call at Day 31. Subjects will be considered to have completed the study after the evaluations at Visit 2. The investigator will recommend the appropriate follow-up medical care, as needed and according to the clinical practice, for all subjects who completed the study.

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

Control drugs (comparator/placebo) or combination drugs are not planned in this study.

4.4 Purpose and timing of interim analyses/design adaptations

An interim analysis is not planned for this study.

[redacted]

4.5 Risks and benefits

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

Comprehensive analytical drug substance comparability studies and ongoing analytical testing of the drug product demonstrate comparability between drug substance/product used in the ongoing Phase III studies (HAWK and HARRIER) and the drug substance intended for commercialization.

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

The risks to subjects in this trial will be minimized by compliance with the eligibility criteria as well as close monitoring.

Women of child bearing potential (WOCBP) and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

The intended commercial formulation has (only in vial) been used in the HAWK extension study (CRTH258A2301E1).

5 Population

The study population will be male and female subjects ≥ 50 years old who are diagnosed with nAMD. Approximately 30 subjects are expected to be injected at approximately 3 sites in the United States of America.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Study eye is diagnosed with nAMD and deemed to be indicated for intravitreal injection at the discretion of the retina specialist.
3. Subjects ≥ 50 years of age at Baseline.

5.2 Exclusion criteria

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

1. Any active intraocular or periocular infection or active intraocular inflammation in either eye at Baseline.
2. Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication or according to Investigator's judgment.
3. Participants legally blind in one or both eyes.
4. History of a medical conditions, ocular or non-ocular, that, in the judgment of the Investigator, would preclude a safe administration of investigational product.

[redacted]

5. Treatment with anti-VEGF intravitreal injection in the study eye within one month prior to enrollment. (Study eye is the eye eligible for intravitreal injection. If both eyes are eligible, one eye should be selected for injection at the discretion of the Investigator and according to clinical practice).
6. The use of intraocular corticosteroids in the study eye during the 3-month period prior to enrollment.
7. Any invasive intraocular surgery, prior long-acting therapeutic agent, or ocular drug release device implantation (approved or investigational) in the study eye any time during the past 3 months.
8. Receipt of any systemic anti-VEGF within the last 6 months prior to enrollment.
9. Intolerance or known reaction to prior biological therapies.
10. Uncontrolled hypertension (systolic > 160 mmHg and/or diastolic > 100 mmHg) while sitting.
11. Current systemic infectious disease or a therapy for active infectious disease.
12. Pregnant or nursing (lactating) women or women of child-bearing potential (WOCBP) is defined as all women less than 1 year postmenopausal or less than 6 weeks since sterilization at Baseline, unless they are using highly effective methods of contraception during dosing of study treatment.

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment. 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 No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

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 (eg age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case

of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

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

6 Treatment

6.1 Study treatment

All subjects will receive one intravitreal injection of brolucizumab 6 mg PFS. A brolucizumab PFS kit will consist of a carton with a sterile sealed blister pack PFS. The IFU will be provided in the carton.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Brolucizumab 6 mg	solution for injection	intravitreal injection	PFS	Novartis

6.1.2 Treatment arms/group

This is an open-label study where all subjects will receive one injection of brolucizumab 6 mg PFS at Baseline.

6.1.3 Treatment duration

One injection of brolucizumab 6 mg PFS per subject will be administered at Baseline, with one End of Study follow up visit after 7 days (± 2 days).

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies administered after the subject was enrolled into the study must be recorded on the appropriate electronic Case Report Forms (eCRF). As needed, treatment of the fellow eye will be performed according to clinical practice and the used medication or procedure should be reported in the eCRF.

6.2.2 Prohibited medication

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

[redacted]

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Anti-VEGF therapy other than IP in study eye	At Baseline	Discontinue study
Intraocular or periocular injections of corticosteroids (except if treatment for AE) in study eye	At Baseline	Discontinue study

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

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

6.3.2 Treatment assignment, randomization

Treatment assignment and randomization is not applicable for this open-label study.

6.4 Treatment masking

This is an open-label study, therefore treatment will be open to subjects, investigator staff, and observational study participants including qualified ophthalmologists and their assistants and representatives of the sponsor.

6.5 Dose escalation and dose modification

Dose escalation and modification is not permitted in this study.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The subject will receive only one intravitreal injection of brolucizumab 6 mg PFS performed by a qualified ophthalmologist. For this injection the appropriate eCRF will be completed.

6.6.2 Emergency breaking of assigned treatment code

Emergency breaking of assigned treatment code is not applicable, since this is an open label study, where each subject receives one injection of brolucizumab 6 mg via PFS.

6.7 Preparation and dispensation

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

[redacted]

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

The study medication has a 2-part label (base plus tear-off label). Immediately before the IVT is performed, site personnel will detach the outer part of the label from the package and affix it to the subject's source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure (IB). Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization 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 investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

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

6.7.2 Instruction for prescribing and taking study treatment

The IVT injection will be carried out under controlled, aseptic conditions per local clinical practice. The study eye will be assessed before and after intravitreal injection to ensure that the procedure and/or the study treatment had not endangered the health of the eye. An IVT injection is contraindicated in subjects with active ocular-or periocular infections and in subjects with active intraocular inflammation; therefore, the investigator should verify that these conditions are not present in either eye (study and fellow eyes) prior to the injection.

All kits of study treatment will be recorded/databased. Date and time of every injection administered to the subject will be recorded in the eCRF.

Additionally, the conduct of IVT injections brolucizumab 6 mg PFS will be observed by an external team under observational protocol [redacted].

[redacted]

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), 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 (eg all of the procedures described in the protocol). The subject will also need to consent that the injection procedure and observation is video recorded. 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 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. New information might require an update to the informed consent 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.

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

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source document.

Subjects should be seen for all visits/assessments as outlined in the Assessment Schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessment of the final visit will be performed. At this final visit, the adverse event and concomitant medications should be recorded on the eCRF.

[redacted]

Table 8-1 Assessment Schedule

Period	Open Label Treatment	Post-Treatment Follow-Up	Follow up
Visit Name	**Baseline**	**End of Study**	**Follow up**
Days	**1**	**8**	**31**
Informed consent	X		
Inclusion / Exclusion criteria	X		
Demography	X		
Medical history/current medical conditions	X		
Concomitant medications	X	X	
Intraocular Pressure (IOP)	X	X	
Vital Signs	X	X	
Pregnancy Test	S		
Study drug administration	X		
Observation of PFS injection	S		
Adverse Events	X	X	S
Ocular Assessments (slitlamp, ophthalmoscopy)	S	S	

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

[redacted]

8.1 Screening

Subjects who sign an informed consent form, meet all of the inclusion and exclusion criteria, will receive one injection of Brolucizumab 6 mg PFS in the study eye at Baseline.

The conduct of the IVT injection and preparation will be observed and videotaped by 2 observers and will follow observational study protocol [redacted], which aims to assess the ability of observational study participants, including qualified ophthalmologists and assistants who may perform the preparation steps, to prepare and administer to subjects an IVT injection using brolucizumab 6 mg PFS and to follow the IFU.

Re-screening is not allowed in this protocol.

8.1.1 Information to be collected on screening failures

There is no separate screening period planned for this study. Subject's Eligibility will be assessed at the Baseline Visit.

Subjects who sign an informed consent but do not receive the IVT injection will be considered a screen failure. The demographic information, informed consent, and Inclusion/Exclusion data must be completed in the eCRF and also be kept in the source documents for screen failure subjects. No further data will be entered into the clinical database for subjects who are screen failures, except if subject experienced a serious adverse event (see SAE section for reporting details).

8.2 Subject demographics/other baseline characteristics

The following data will be documented in the source document: age, sex, race, ethnicity, vital signs, study eye, IOP, date of nAMD diagnosis, concomitant medications, medical history, and current medical conditions.

8.3 Efficacy

Efficacy is not measured in this study. The usability assessments of PFS conducted within this study are specified in observational study protocol [redacted]

8.4 Safety

Safety evaluation will include ocular and non-ocular assessments (eg vital signs, IOP, slitlamp and ophthalmoscopy) and will be performed according to the clinical practice. Any clinically significant changes should be reported as AEs.

For details on AE collection and reporting, refer to Section 10.1.1.

The End of Study visit after 7 days (± 2) will be done at the site. The ocular assessments like slitlamp and ophthalmoscopy will be recorded in the source document and IOP will be entered in the eCRF. The non-ocular assessment (vital signs) will be recorded in the eCRF.

[redacted]

Additionally, a follow-up phone call 30 days after the End of Study Visit will be performed for subjects with any ongoing AEs at the End of Study Visit. Any occurred adverse events in this period should be collected in the source, and SAEs must be reported to Novartis safety according instructions in Section 10.1.3.

8.4.1 Pregnancy and assessments of fertility

A urine pregnancy test will be conducted for all women of childbearing potential to assess pregnancy before inclusion in the study.

Additional pregnancy testing may be performed if requested by local requirements.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

This is a single dose study, therefore discontinuation of study treatment is not applicable.

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

If the subject cannot or is unwilling to attend the follow up visit at Day 8, 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.

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 (eg telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

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.

[redacted]

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

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, eg dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for 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 (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject’s interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs / IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their End of Study Visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

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 (eg, 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.

[redacted]

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

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

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

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

- no action taken (further observation only)
- Concomitant medication or non-drug therapy given.

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

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

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

Adverse event monitoring should be continued for at least 30 days, following the injection.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (eg continuing at the end of the study), and assessment must be made at each visit

[redacted]

(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).

10.1.2 Serious adverse events

A serious adverse event (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, eg defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

[redacted]

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 following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a chief medical officer & 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 European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Safety events occurring during the study will be reported as AEs in the eCRF. Device malfunction observations are to be reported to the respective Novartis Country Organization Quality Assurance.

10.1.4 Pregnancy reporting

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

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

10.2 Additional Safety Monitoring

No additional safety monitoring is planned in this study.

[redacted]

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the 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 electronic data capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

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

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

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

11.2 Database management and quality control

Novartis personnel or designated Contract Research Organization (CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated 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 (ATC) classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit a Novartis representative will review the protocol and data capture requirements (ie eSource direct data entry (DDE) or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture/data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to

[redacted]

specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments, including the secure digital (SD) card, properly labelled with the subject number, containing the video taken from the injection procedure. 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

12.1 Analysis sets

The Full Analysis Set (FAS) includes all enrolled subjects who receive a dose of study treatment.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data will be listed and summarized descriptively for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term for all subjects.

12.3 Treatments

Descriptive summary statistics for exposure to study treatment will be provided for the FAS. The cumulative number of IVT injections will be presented for the period baseline to Day 8.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system for all subjects.

[redacted]

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

Incidence of ocular and non-ocular AEs are considered primary endpoints.

12.4.2 Statistical model, hypothesis, and method of analysis

No formal hypothesis tests will be performed in this study. All safety analyses will be performed using the FAS.

Adverse events

The number (and percentage) of subjects with treatment-emergent adverse events (events started after the single dose of study treatment or events present prior to start of study 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 the study. Separate presentations will be provided related to ocular events in the study eye and fellow eye and systemic events. Additional summaries will be provided by severity and causality (separately assessed for the injection procedure and the drug). 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.

Ophthalmic examinations

Pre-injection and post-injection IOP measurements will be listed.

Vital signs

All vital signs data will be listed by subject and, if ranges are available, abnormalities will be flagged with thresholds representing clinical relevant abnormality.

12.4.3 Handling of missing values/censoring/discontinuations

This is a single dose, open-label study with two scheduled visits over the period of one week. Therefore, missing data will not be imputed. Analysis of the primary endpoint will include all subjects in the FAS as defined in Section 12.1.

12.4.4 Sensitivity and Supportive analyses

This section is not applicable.

[redacted]

12.5 Analysis of secondary endpoints

Based on the study design, analysis of secondary endpoints is not applicable.

12.6 Interim analyses

No interim analysis is planned for this study.

12.7 Sample size calculation

12.7.1 Primary endpoint(s)

No formal statistical power calculations to determine sample size were performed for this study.

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 (eg, advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis/ Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

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

[redacted]

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

14.1 Protocol Amendments

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

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

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

[redacted]

15 References

References are available upon request

Blinder KJ, Bradley S, Bressler NM, et al (2003) Effect of lesion size, visual acuity, and lesion composition on visual acuity change with and without verteporfin therapy for choroidal neovascularization secondary to age-related macular degeneration: TAP and VIP report no. 1. Am. J. Ophthalmol. p. 407-18.

Bloch SB, Larsen M, Munch IC (2012) Incidence of legal blindness from age-related macular degeneration in denmark: year 2000 to 2010. Am. J. Ophthalmol. p. 209-213.e2.

Campbell JP, Bressler SB, Bressler NM (2012) Impact of availability of anti-vascular endothelial growth factor therapy on visual impairment and blindness due to neovascular age-related macular degeneration. Arch. Ophthalmol. p. 794-5.

Ferris FL (1983) Senile macular degeneration: review of epidemiologic features. Am. J. Epidemiol. p. 132-51.

Ferris FL, Fine SL, Hyman L (1984) Age-related macular degeneration and blindness due to neovascular maculopathy. Arch. Ophthalmol. p. 1640-2.

Kawasaki R, Yasuda M, Song SJ, et al (2010) The prevalence of age-related macular degeneration in Asians: a systematic review and meta-analysis. Ophthalmology p. 921-7.

Lim LS, Mitchell P, Seddon JM, et al (2012) Age-related macular degeneration. Lancet p. 1728-38.

Miller JW (2013) Age-related macular degeneration revisited--piecing the puzzle: the LXIX Edward Jackson memorial lecture. Am. J. Ophthalmol. p. 1-35.e13.

Rein DB, Wittenborn JS, Zhang X, et al (2009) Forecasting age-related macular degeneration through the year 2050: the potential impact of new treatments. Arch. Ophthalmol. p. 533-40.

Shah AR, Del Priore LV (2009) Natural history of predominantly classic, minimally classic, and occult subgroups in exudative age-related macular degeneration. Ophthalmology p. 1901-7.

Shah AR, Del Priore LV (2007) Progressive visual loss in subfoveal exudation in age-related macular degeneration: a meta-analysis using Lineweaver-Burke plots. Am. J. Ophthalmol. p. 83-89.

Smith W, Assink J, Klein R, et al (2001) Risk factors for age-related macular degeneration: Pooled findings from three continents. Ophthalmology p. 697-704.

Sommer A, Tielsch JM, Katz J, et al (1991) Racial differences in the cause-specific prevalence of blindness in east Baltimore. N. Engl. J. Med. p. 1412-7.

Spilsbury K, Garrett KL, Shen WY, et al (2000) Overexpression of vascular endothelial growth factor (VEGF) in the retinal pigment epithelium leads to the development of choroidal neovascularization. Am. J. Pathol. p. 135-44.

[redacted]

Wong TY, Wong T, Chakravarthy U, et al (2008) The natural history and prognosis of neovascular age-related macular degeneration: a systematic review of the literature and meta-analysis. Ophthalmology p. 116-26.

[redacted]

16 Appendices

Appendices are not applicable for this study.

[redacted]