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| PROTOCOL | |
| **BROLUCIZUMAB TREATMENT FOR PIGMENT EPITHELIAL DETACHMENT IN TREATMENT-RESISTANT NEOVASCULAR AGE RELATED MACULAR DEGENERATION** | |
| investigatorS | **A/Prof Andrew Chang**  **Dr James Wong**  **A/Prof Samantha Fraser-Bell**  **Dr Thomas Pham**  **Dr Yasser Tariq** |
| STudy drug | **Intravitreal Brolucizumab Injection (6.0mg)** |
| INDICATION STUDIED | **Neovascular Age-Related Macular Degeneration** |
| Version number | **1.2** |
| release date | **4 March 2021** |
| Investigator agreement: | I have read the clinical study described herein, recognise its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practices (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, and all regulatory requirements. |

**Principal Investigator: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

Signature Date

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1. **SYNOPSIS**

**Sponsor:** Sydney Retina Clinic & Day Surgery

187 Macquarie Street, Sydney, NSW, 2000

**Protocol Number: C**RTH258AAU04T

**Study Drug:** Brolucizumab Injection (6.0mg), formerly RTH258

**Title of Study:** Brolucizumab Treatment for Pigment Epithelial Detachment in Treatment-Resistant Neovascular Age-Related Macular Degeneration.

**Objectives:** The aim of the study is to evaluate the effectiveness of intravitreal brolucizumab in the treatment of PED’s secondary to neovascular macular degeneration among treatment-resistant patients.

**Primary:**

To evaluate the resolving and reducing effects of brolucizumab on PED’s in a cohort of treatment resistant eyes:

* Mean change in PED height at weeks 24 and 52 compared to the baseline.
* Proportion of patients with resolution of PED at 24 and 52 weeks

**Secondary Objectives:**

To evaluate concurrent changes in visual and anatomic outcomes.:

* Proportion of patients who have no fluid on SD-OCT at weeks 12, 24 and 52.
* Mean structural changes of PED on OCT-Angiography.
* Mean change in visual acuity at weeks 12, 24 and 52 compared to the baseline.
* Proportion of patients who gain 5, 10 and 15 letters OR with BCVA better than 20/40 at weeks 12, 24 and 52
* Mean change in central foveal thickness and volume measured by SD-OCT at weeks 12, 24 and 52 compared to the baseline.
* Proportion of patients with development of macular atrophy at week 52.
* The change of retinal function measured by Macular Integrity Assessment (MAIA) at weeks 24 and 52 compared to the baseline.
* Mean change in [National Eye Institute Visual Functioning Questionnaire-25](http://www.nei.nih.gov/resources/visionfunction/vfq_ia.pdf) (NEI VFQ-25)score between baseline and weeks 24 and 52.
* Incidence and severity of adverse events over study period.

**Study Design:** This is a prospective, open-labelled study in patients with neovascular macular degeneration.All subjects will receive 6.0mg of intravitreal brolucizumab every 4 weeks between baseline and week 8. Following these loading doses, a disease activity assessment will be performed at week 16.

**Disease Activity Criteria at Week 16:**

* Decrease in BCVA of ≥ 5 letters compared with Baseline
* Decrease in BCVA of ≥ 3 letters and CSFT increase ≥ 75μm compared with Week 12
* Decrease in BCVA of ≥ 5 letters **due to neovascular AMD disease activity** compared with Week 12
* New or worse intraretinal cysts (IRC) /intraretinal fluid (IRF) compared with Week 12

If a subject meets any of the above disease criteria at week 16, the subject will be assigned to receive injections every 8 weeks (q8w) thereafter, up to study exit (Week 16, 24, 32, 40 and 48).

If a subject does not meet any of the above disease activity criteria, the subject will be injected every 12 weeks (q12w) up to study exit (week 20, 32 and 44).

**Population:** Fifty five eligible subjects will be recruited from Sydney Retina. All assessments and treatments will be performed at Sydney Retina.

**Study Duration:** The study will be conducted over 18 months (6-month recruitment period and 12-month treatment and follow up period).

Inclusion Criteria:

* Subjects must give written informed consent before any study related procedures are performed
* Subjects must be 50 years of age or older at baseline
* Pigment epithelial detachment (PED) secondary to neovascular macular degeneration. PED is defined as a discrete or localised dome-shaped or irregular elevation of the RPE on SD-OCT that was optically empty (i.e. serous) with a focus of neovascularisation at the edge or that was comprised of heterogeneous tissue of mixed reflectivity or layering within the sub-PED compartment.
* Previously treated neovascular age-related macular degeneration, “treatment resistance” is defined as eyes with persistent active/exudation despite at least 4 previous ranibizumab and/or aflibercept treatments in the 6 months prior to baseline, not including loading dose, with a minimal interval of 8 weeks between the last anti-VEGF injection and the baseline injection
* Best corrected baseline visual acuity between 20-78 letters on ETDRS chart (Snellen equivalent 6/12 to 6/120) in the study eye.
* Active CNV lesions secondary to AMD that affect the central subfield (excluding retinal angiomatous proliferation [RAP] and polypoidal vasculopathy [PCV]) in the study eye, confirmed by the angiography and Principal Investigator.
* Total area of CNV must comprise >50% of the total lesion area in the study eye.
* Intra and or subretinal fluid affecting the central subfield of the study eye.

Exclusion Criteria:

* Any active intraocular or periocular infection or active intraocular inflammation (eg, infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis) in either eye at Baseline
* Central subfield of the study eye affected by fibrosis or geographic atrophy assessed by colour fundus photography autofluorescence.
* Total area of fibrosis ≥ 50% of the total lesion in the study eye
* Subretinal blood affecting the central subfield and/or ≥ 50% of the lesion of the study eye
* Subject has received any investigational treatment for neovascular AMD (other than vitamin supplements) in the study eye at any time
* Eyes diagnosed with Retinal Angiomatous Proliferation or Polypoidal Choroidal Vasculopathy lesion
* Any history or evidence of a concurrent intraocular condition in the study eye, including retinal diseases other than neovascular AMD, that, in the judgment of the Investigator, could either require medical or surgical intervention during the course of the study to prevent or treat visual loss that might result from that condition or that limits the potential to gain visual acuity upon treatment with the investigational product
* Retinal pigment epithelium (RPE) rip/tear in the study eye at Baseline
* Current vitreous haemorrhage or history of vitreous haemorrhage in the study eye within 4 weeks prior to Baseline
* History or evidence of the following in the study eye:
* Previous photodynamic therapy (PDT)
* Intraocular or refractive surgery within the 90-day period prior to Baseline
* Previous penetrating keratoplasty or vitrectomy
* Previous panretinal photocoagulation
* Previous submacular surgery, other surgical intervention or laser treatment for AMD
* Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication or according to Investigator’s judgment at Baseline
* Aphakia and/or absence of the posterior capsule in the study eye at Screening or Baseline
* Intra- or periocular use of corticosteroids in the study eye during the 6-month period prior to Baseline
* Use of topical ocular corticosteroids in the study eye for 60 or more consecutive days within the 90-day period prior to Baseline
* Use of systemic corticosteroids for 30 or more consecutive days within the 90 days prior to Baseline, with the exception of low stable doses of corticosteroids (defined as ≤10 mg prednisolone or equivalent dose used for 90 days or more). Inhaled, nasal or dermal steroids are also permitted
* Previous therapeutic radiation near the region of the study eye
* History of a medical condition (disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding) that, in the judgment of the Investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product
* History of hypersensitivity to any component of the test article, control article, or clinically relevant sensitivity to fluorescein dye (or indocyanine green), as assessed by the Investigator
* Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until termination of gestation, confirmed by a positive hCG pregnancy test and women of child-bearing potential, defined as all women less than 1 year postmenopausal or less than 6 weeks since sterilization at Baseline, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
* Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception
* Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before Baseline. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
* Male sterilization (at least 6 months prior to Baseline). For female subjects in the study, the vasectomized male partner should be the sole partner for that subject
* Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
* Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception
* Placement of an intrauterine device (IUD) or intrauterine system (IUS)
* Participation in an investigational drug, biologic, or device study within 30 days or the duration of 5 half-lives of the investigational product (whichever is longer) prior to Baseline *Note: observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary*
* Systemic anti-vascular endothelial growth factor (VEGF) therapy within the 90-day period prior to Baseline
* Stroke or myocardial infarction in the 90-day period prior to Baseline
* Uncontrolled blood pressure defined as a systolic value ≥ 160 mmHg or diastolic value ≥ 100 mmHg at Screening

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

**Definition of pigment epithelial detachment (PED):**

Pigment epithelial detachment was defined as a discrete or localized dome-shaped or irregular elevation of the RPE on OCT that was optically empty (i.e., serous) with a focus of neovascularization at the edge or that was comprised heterogeneous tissue of mixed reflectivity or layering within the sub-PED compartment.

**Evaluation Schedule:**

* BCVA and SD-OCT measurements will be performed at baseline and each follow-up visit.
* Colour fundus photos and OCT-A will be conducted at baseline, weeks 12, 24, 36 and 52
* Fluorescein and indocyanine angiography will be performed at baseline, weeks 24 and 52
* MAIA and NEI VFQ-25 will be conducted at baseline, weeks 24 and 52.

**Assessments:**

**Efficacy:**

* BCVA using ETDRS Methodology
* Spectral domain optical coherence tomography (SD-OCT)
* Optical coherence tomography angiography (OCT-A)
* Fluorescein angiography
* Macular Integrity Assessment (MAIA)
* National Eye Institute Visual Function Questionnaire-25 (VFQ-25)

**Safety:**

* Vital signs
* Complete ophthalmic exam:
* Slit-lamp exam
* IOP measurement (pre/post injections)
* Dilated fundus exam
* Post-injection assessments
* Treatment emergent adverse events

**Diagnostic:**

* Colour fundus photography
* Fundus autofluorescence
* Indocyanine green angiography (ICG)

**Ethics and Good Clinical Practice:**

This study will be performed according to principles of Good Clinical Practice (GCP) [Chapter 2 of the ICH Harmonized Tripartite Guideline for GCP], the declaration of Helsinki, and national laws and regulations about clinical studies. Ethical approval will be obtained from a registered human research ethics committee (Bellberry).

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1. introduction

**1.1 Background**

Retinal pigment epithelial detachments (PEDs) are associated with many retinal diseases, including neovascular age-related macular degeneration (AMD), can cause significant vision loss, and are difficult to treat. Pigment epithelial detachments are seen in up to 62% of patients with advanced neovascular AMD (1). The pathogenesis underlying PEDs is complex and not completely understood (2), the most likely scenario involves displacement of the RPE by exudation from choroidal neovascularization (CNV) (3). PED at baseline has been shown to be a predictor of vision loss in patients with AMD (4). Approximately 50% of patients with newly diagnosed PEDs will experience significant loss in visual acuity (>3 lines) 1 year from diagnosis without treatment (5). Thus, PEDs are an important marker of disease severity and progression in neovascular AMD.

The Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (6) established the efficacy of intravitreal ranibizumab therapy (Lucentis; Genentech, Inc., South San Francisco, CA) in improving visual and anatomic outcomes in patients with neovascular AMD. At 24 months in this study, 26% to 33% of ranibizumab-treated patients, gained 15 letters or more in best-corrected visual acuity (BCVA) from baseline. In these patients with neovascular AMD, ranibizumab was associated with arrested or decreased growth of and leakage from choroidal neovascularization (CNV). In other studies of patients with neovascular AMD, the subgroups with PED have been associated with worse visual acuity outcomes (4).

Currently, there are few prospective studies that demonstrate effective therapy for PEDs associated with neovascular AMD. These analyses are limited by the use of time-domain optical coherence tomography (OCT) or do not focus specifically on eyes with PED, providing incomplete information regarding PED outcomes (7-9). The Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intraocular Ranibizumab study (10, 11) evaluated an OCT-guided dosing regimen with ranibizumab 0.5 mg for the treatment of patients with neovascular AMD. This study found no correlation between PED at baseline or 3 months with visual acuity at 12 months. Additionally, limited data are available on the use of higher doses (2.0 mg) of anti-VEGF’s to treat PEDs. Chan et al (12) hypothesized that a greater concentration of ranibizumab may penetrate the retinal pigment epithelial (RPE) barrier and suppress CNV, leading to more rapid resolution of the PED. Although visual acuity outcomes were no different at 12 months between the 2.0-mg and 0.5-mg arms, the 2.0-mg regimen did result in more rapid reductions in percentage of PED height.

Brolucizumab (RTH258) RTH258, formerly known as ESBA1008, is a humanized single-chain Fv (scFv) antibody fragment inhibitor of VEGF with a molecular weight of ~26 kDa that is being developed for the treatment of CNV associated with neovascular AMD. It is an inhibitor of VEGF-A and works by binding to the receptor binding site of the VEGF-A molecule, thereby preventing the interaction of VEGF-A with its receptors VEGFR1 and VEGFR2 on the surface of endothelial cells. Increased levels of signalling through the VEGF pathway are associated with pathologic ocular angiogenesis and retinal oedema. Inhibition of the VEGF pathway has been shown to inhibit the growth of neovascular lesions and resolve retinal oedema in patients with neovascular AMD.

In an ascending single dose study, Alcon protocol C-10-083, several doses of RTH258 (0.5, 3.0, 4.5 and 6 mg), were evaluated versus ranibizumab 0.5 mg with regard to the mean change from Baseline to Month 1 in central subfield thickness (CSFT) as measured by spectral- domain optical coherence tomography (SD-OCT) (primary efficacy endpoint). Treatment with RTH258 provided similar reductions for all doses in CSFT to ranibizumab. The primary statistical analysis compared RTH258 4.5 mg and 6.0 mg versus ranibizumab 0.5 mg with both doses achieving noninferiority. Notable however was the median time to receiving standard of care which was longer for the RTH258 3.0 mg, 4.5 mg and 6.0 mg doses (75 days in the 6.0 mg group compared with 45 days in the ranibizumab group), suggesting a longer duration of treatment effect. RTH258 6 mg was the highest dose tested in the study and no unexpected safety issues were reported that would preclude further clinical development.

Subsequently the safety and efficacy of the RTH258 6 mg dose were evaluated versus aflibercept 2 mg in a 56 week multiple dose study (Alcon protocol C-12-006) with a primary endpoint at 12 weeks. The efficacy data from this study showed that RTH258, when it was given every 8 weeks (q8), was as effective as the active control in terms of BCVA change from Baseline. There were numerical advantages with RTH258 over aflibercept with regard to the change in CSFT from Baseline. The majority (72%) of the RTH258 treated subjects who completed an extension of the study, who received treatment every 12 weeks (q12), showed visual stability. There were no adverse events in the RTH258 group that negatively(13, 14).

There are, as yet, no established treatment recommendations for PED associated with CNV, most likely due to the fact that the development of PED and its natural course in AMD has not yet been fully investigated. In general, treatment of PEDs associated with CNV is particularly difficult due to the risk of development of an RPE tear (15). Treatment options for CNV associated with PED in AMD, such as laser photocoagulation, photodynamic therapy, and/or intravitreal steroids, have been reported but lead to unsatisfactory or conflicting results. The effect of anti-VEGF therapy on PEDs is as yet, unclear.

Optical coherence tomography (OCT) is a non-invasive imaging method appropriate for identifying morphological macular changes, and widely used to evaluate and monitor the efficacy of anti-VEGF therapies in these patients. The aim of this study is to assess the effect of anti-VEGF therapy, namely brolucizumab, on the morphology and functionality of PEDs secondary to AMD.

**1.2 Study Rationale**

This study is designed to specifically target subjects with PED secondary to neovascular macular degeneration. This study will aim to describe the effects of brolucizumab on baseline PED status and height as well as visual and anatomic outcomes in patients with neovascular AMD treated with brolucizumab on a fixed dosing regimen according to the product label.

* 1. **Benefits and risks**

Brolucizumab is an inhibitor of VEGF with a mechanism of action similar to ranibizumab but with a smaller molecular size (26 kDa and 48 kDa respectively). Nonclinical studies have demonstrated that RTH258 is at least as potent as ranibizumab, with a similar vitreal half-life and a significantly lower systemic exposure. The low systemic exposure should confer a good safety profile even at a high dose. The higher dose, similar half-life, and potency of RTH258 may confer a longer treatment duration compared to currently available treatments. Two clinical studies, C-10-083 and C-12-006, have demonstrated that RTH258 is as effective as ranibizumab and aflibercept in improving BCVA outcomes whilst having a reduced treatment frequency, thus providing a potential benefit to patients and their caregivers/physicians. The ocular and systemic safety profile of single or repeated doses of RTH258 were also evaluated in the C-10-083 and C-12-006 studies, respectively, and demonstrated similar safety profiles to ranibizumab and aflibercept. Further details of the known and potential risks and benefits associated with RTH258 are presented in the Investigator’s Brochure.

Summarized, the results from the Phase 2 studies demonstrate that brolucizumab has similar efficacy to currently available treatment options with potentially greater duration. These data support the further development of RTH258 with a treatment regimen including q12 maintenance dosing.

**1.4 Ethics**

This clinical study will be conducted in accordance with the principles of the Declaration of Helsinki, and in compliance with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) Consolidated Guideline and other regulations as applicable. The Investigator and all clinical study staff will conduct the clinical study in compliance with the protocol. The Investigator will ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience.

Before clinical study initiation, this protocol, the informed consent form (ICF), any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an Independent Ethics Committee/Institutional Review Board (IEC/IRB). The Investigator must provide documentation of the IEC/IRB approval to the Novartis. The approval must be dated and must identify the applicable protocol, amendments (if any), ICF, all applicable recruiting materials, written information for subject, and subject compensation programs. The IEC/IRB must be provided with a copy of the Investigator’s Brochure, any periodic safety updates, and all other information as required by local regulation and/or the IEC/IRB. At the end of the study, the Investigator will notify the IEC/IRB about the study’s completion. The IEC/IRB will also be notified if the study is terminated prematurely. Finally, the Investigator will report to the IEC/IRB on the progress of the study at intervals stipulated by the IEC/IRB.

Voluntary informed consent will be obtained from every subject (and/or legal representative, as applicable) prior to the initiation of any screening or other study related procedures. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or designee, will explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved ICF. The subject must be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel. The Investigator must provide the subject with a copy of the ICF written in a language the subject understands. The ICF must meet all applicable local laws and will provide subjects with information regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with the investigational product, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Subjects will be told about the voluntary nature of participation in the study and will be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject also will be told that their records may be accessed by appropriate authorities and Novartis designated personnel. The Investigator must keep the original, signed copy of the ICF and must provide a duplicate copy to each subject.

**PROTOCOL AMENDMENTS**

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments must be approved by the IEC/IRB prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Amendments may necessitate that the ICF and other study-related material be revised. If the ICF is revised, all subjects currently enrolled in the study may be required by the IEC/IRB to sign the approved, revised ICF.

# 2. OBJECTIVES

The aim of the study is to evaluate the resolving and reducing effects of intravitreal brolucizumab in the treatment of PED’s secondary to neovascular macular degeneration.

**2.1 Primary Objective**

To evaluate the resolving and reducing effects of brolucizumab on PED’s in a cohort of treatment resistant eyes:

* Mean change in PED height at weeks 24 and 52 compared to the baseline.
* Proportion of patients with resolution of PED at 24 and 52 weeks

**2.2 Secondary Objectives**

To evaluate changes in various visual and anatomical outcomes.

* Proportion of patients who have no fluid on SD-OCT at weeks 12 24 and 52.
* Mean structural changes of PED on OCT-Angiography.
* Mean change in visual acuity at weeks 12, 24 and 52 compared to the baseline.
* Proportion of patients who gain 5, 10 and 15 letters OR with BCVA better than 20/40 at weeks 12, 24 and 52
* Mean change in central foveal thickness and volume measured by SD-OCT at weeks 12, 24 and 52 compared to the baseline.
* Proportion of patients with development of macular atrophy at week 52.
* The change of retinal function measured by Macular Integrity Assessment (MAIA) at weeks 24 and 52 compared to the baseline.
* Mean change in National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) score between baseline and weeks 24 and 52.
* Incidence and severity of adverse events over study period.

3. study design

# 3.1 Description of the Study

This is a prospective, open-labelled study in patients with pigment epithelial detachment (PED) secondary to neovascular macular degeneration. All subjects will receive 6.0mg of intravitreal brolucizumab every 4 weeks between baseline and week 8 (3 loading doses), and subsequently receive 6.0mg of intravitreal brolucizumab every 8 or 12 weeks for the remainder of the study period (weeks 52).

Fifty five subjects who meet the inclusion/exclusion criteria will be recruited from Sydney Retina Clinic and followed up for 52 weeks. All assessments and treatments will be performed at Sydney Retina Clinic. All eligible subjects will initially receive 3 monthly loading doses of 6.0mg of intravitreal brolucizumab injection. Following these loading doses, a disease activity assessment will be performed at week 16.

**Disease Activity Criteria at Week 16:**

* Decrease in BCVA of ≥ 5 letters compared with Baseline
* Decrease in BCVA of ≥ 3 letters and CSFT increase ≥ 75μm compared with Week 12
* Decrease in BCVA of ≥ 5 letters **due to neovascular AMD disease activity** compared with Week 12
* New or worse intraretinal cysts (IRC) /intraretinal fluid (IRF) compared with Week 12

If a subject meet any of the above disease criteria at week 16, the subject will be assigned to receive injections every 8 weeks (q8w) thereafter, up to study exit (Week 16, 24, 32, 40 and 48).

If a subject does not meet any of the above disease activity criteria, the subject will be injected every 12 weeks (q12w) up to study exit (week 20, 32 and 44).

**3.2 Outcome Measures**

3.2.1 Primary Outcome Variables

* To evaluate the effect of presence and height of baseline PED at weeks 24 and 52.
* Proportion of patients with resolution of PED at weeks 24 and 52.

3.2.2 Secondary Outcome Variables

* Structural changes of PED on OCT-Angiography
* Best corrected ETDRS visual acuity
* Central foveal thickness (RPE to ILM) and volume measured by SD-OCT
* Retinal function assessed with MAIA
* HRQoL by NEI VFQ-25 questionnaires

**3.3 Safety Plan**

Each subject will be instructed to contact the study staff if he or she experiences any adverse events. All adverse events (serious and non-serious) will be recorded during study period. The Principal Investigator will review all adverse events on an ongoing basis. The Bellberry Human Research Ethics Committee will be notified of any interruption in enrolment or change in the conduct of the study.

Any subject who develops significantly raised IOP (≥ 30 mmHg) at any time during the study will be monitored according to the physician’s clinical judgment and may undergo additional measurements of IOP beyond those specified in the protocol.

Study drug administration will be held for subjects who experience certain ocular events or infection events. In the event any subject develops an adverse event in the study eye that is considered by the designated evaluating physician to be severe in intensity, serious consideration should be given to withdrawing the subject from the study. Subjects withdrawn from the study prior to completion will be asked to return for an early termination evaluation 28 days (± 7 days) following their last injection/study visit for monitoring of all adverse events (serious and non-serious; ocular and non-ocular).

The process for safety monitoring and reporting is further detailed in Section 5.

4. MATERIALS AND METHODS

# 4.1 Subjects

Fifty five subjects will be enrolled from Sydney Retina. All assessments and treatments will be performed at Sydney Retina. All subjects will receive monthly 6.0 mg intravitreal brolucizumab injection for the first 3 months followed by either 3 or 5 injections for the next 10 months, dependent on disease activity at week 16.

* + 1. **Inclusion Criteria**
* Subjects must give written informed consent before any study related procedures are performed
* Subjects must be 50 years of age or older at baseline
* Age 50 years or older
* Pigment epithelial detachment (PED) secondary to neovascular macular degeneration. PED is defined as a discrete or localised dome-shaped or irregular elevation of the RPE on SD-OCT that was optically empty (i.e. serous) with a focus of neovascularisation at the edge or that was comprised of heterogeneous tissue of mixed reflectivity or layering within the sub-PED compartment.
* Previously treated neovascular age-related macular degeneration, “treatment resistance” is defined as eyes with persistent active/exudation despite at least 4 previous ranibizumab and/or aflibercept treatments in the 6 months prior to baseline, not including loading dose, with a minimal interval of 8 weeks between the last anti-VEGF injection and the baseline injection.Best corrected baseline visual acuity between 20-73 letters on ETDRS chart (Snellen equivalent 6/12 to 6/120) in the study eye.
* Active subfoveal lesions with classic CNV, some classic CNV component, or purely occult CNV; total area of lesion less than 12-disc areas, and total CNV area constituting 50% or more of total lesion area based on fluorescein angiography.
* Total area of CNV must comprise >50% of the total lesion area in the study eye.
* Intra and or subretinal fluid affecting the central subfield of the study eye.

4.1.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

* Any active intraocular or periocular infection or active intraocular inflammation (eg, infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis) in either eye at Baseline
* Central subfield of the study eye affected by fibrosis or geographic atrophy assessed by colour fundus photography autofluorescence.
* Total area of fibrosis ≥ 50% of the total lesion in the study eye
* Subretinal blood affecting the central subfield and/or ≥ 50% of the lesion of the study eye
* Subject has received any investigational treatment for neovascular AMD (other than vitamin supplements) in the study eye at any time
* Eyes diagnosed with Retinal Angiomatous Proliferation or Polypoidal Choroidal Vasculopathy lesion
* Any history or evidence of a concurrent intraocular condition in the study eye, including retinal diseases other than neovascular AMD, that, in the judgment of the Investigator, could either require medical or surgical intervention during the course of the study to prevent or treat visual loss that might result from that condition or that limits the potential to gain visual acuity upon treatment with the investigational product
* Retinal pigment epithelium (RPE) rip/tear in the study eye at Baseline
* Current vitreous haemorrhage or history of vitreous haemorrhage in the study eye within 4 weeks prior to Baseline
* History or evidence of the following in the study eye:
* Previous photodynamic therapy (PDT)
* Intraocular or refractive surgery within the 90-day period prior to Baseline
* Previous penetrating keratoplasty or vitrectomy
* Previous panretinal photocoagulation
* Previous submacular surgery, other surgical intervention or laser treatment for AMD
* Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication or according to Investigator’s judgment at Baseline
* Aphakia and/or absence of the posterior capsule in the study eye at Screening or Baseline
* Intra- or periocular use of corticosteroids in the study eye during the 6-month period prior to Baseline
* Use of topical ocular corticosteroids in the study eye for 60 or more consecutive days within the 90-day period prior to Baseline
* Use of systemic corticosteroids for 30 or more consecutive days within the 90 days prior to Baseline, with the exception of low stable doses of corticosteroids (defined as ≤10 mg prednisolone or equivalent dose used for 90 days or more). Inhaled, nasal or dermal steroids are also permitted
* Previous therapeutic radiation near the region of the study eye
* History of a medical condition (disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding) that, in the judgment of the Investigator, would preclude scheduled study visits, completion of the study, or a safe administration of investigational product
* History of hypersensitivity to any component of the test article, control article, or clinically relevant sensitivity to fluorescein dye (or indocyanine green), as assessed by the Investigator
* Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until termination of gestation, confirmed by a positive hCG pregnancy test and women of child-bearing potential, defined as all women less than 1 year postmenopausal or less than 6 weeks since sterilization at Baseline, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
* Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception
* Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before Baseline. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
* Male sterilization (at least 6 months prior to Baseline). For female subjects in the study, the vasectomized male partner should be the sole partner for that subject
* Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
* Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception
* Placement of an intrauterine device (IUD) or intrauterine system (IUS)
* Participation in an investigational drug, biologic, or device study within 30 days or the duration of 5 half-lives of the investigational product (whichever is longer) prior to Baseline *Note: observational clinical studies solely involving over-the-counter vitamins, supplements, or diets are not exclusionary*
* Systemic anti-vascular endothelial growth factor (VEGF) therapy within the 90-day period prior to Baseline
* Stroke or myocardial infarction in the 90-day period prior to Baseline
* Uncontrolled blood pressure defined as a systolic value ≥ 160 mmHg or diastolic value ≥ 100 mmHg at Screening

**Definition of pigment epithelial detachment (PED):**

Pigment epithelial detachment was defined as a discrete or localized dome-shaped or irregular elevation of the RPE on OCT that was optically empty (i.e., serous) with a focus of neovascularization at the edge or that was comprised heterogeneous tissue of mixed reflectivity or layering within the sub-PED compartment.

**4.1.3 Patient Withdrawal**

Patients may withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. If a patient withdraws from study participation, any known reason for withdrawal should be documented in the database. All information already collected as part of the study will be retained for analysis; however, no further efforts will be made to obtain or record additional information regarding the patient.

Reasons for subject discontinuation may include, but are not limited to, the following:

* Loss to follow-up
* Pregnancy
* Non-study intervention for CMO in the study eye
* Safety concerns
* Rescue photodynamic therapy
* Death
* Rhegmatogenous retinal detachments
* Stage 3 or 4 macular holes

If a subject discontinues from the study, he or she will not be allowed to re‑enter the study.

**4.2 Study Drug**

Intravitreal brolucizumab will be supplied Novartis Australia.

All patients will receive 6.0mg intravitreal brolucizumab injection. The study drug will be injected intravitreally using an aseptic technique. Blood pressure will be measured before and 15 min after the procedure.

**4.2.1 Packaging, Labeling and Storage**

Beovu 120mg/mL solution for injection in pre-filled syringe. Each pre-filled syringe contains 19.8mg of brolucizumab in 0.165mL solution. This provides a usable amount to deliver a single dose of 0.05mL containing 6mg of brolucizmab. For study drug in vials, the study drug will be withdrawn using aseptic technique.

Study drug will be shipped to the site via overnight shipping using cold packs to maintain a temperature of 2° to 8° C. The Investigator, or an approved representative (e.g. study coordinator), will ensure that all study drugs are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. The shipping box is to be opened and stored immediately at the site in a refrigerator intended for investigational products at a temperature of 2° to 8°C.

When vials are removed from the refrigerator, the solution should be visually inspected and it should have no evidence of turbidity. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Exposure of the material to temperatures outside these limits, except for warming prior to administration, is not recommended and may result in loss of activity. Records of actual storage conditions (i.e. temperature log) at the study site must be maintained; and must include a record of the dates, when the refrigerator was checked, the initials of person checking, and the temperature.

**4.2.2 Supply and Disposition of Drug**

Study drug will be shipped to the Investigator or designee at regular intervals or as needed during the study. At the end of the study and following reconciliation and documentation, all used vials will be destroyed at the site.

**4.2.3 Drug Accountability**

The Investigator is responsible for the accountability of all used and unused study drug. Drug accountability records must be kept current. These records should contain the dates, quantities and identification numbers (or lot numbers) of study drug received by the Investigator, dispensed or administered to specified subjects, returned from subjects (if applicable), disposed of at the site.

**4.3 Study Drug Administration**

The intravitreal injection procedure using the pre-filled syringe should be carried out under controlled aseptic conditions. Adequate anaesthesia and a broad-spectrum microbicide should be given prior to the injection. Using aseptic technique, The study drug will be given by intravitreal injection 3.5 to 4mm posterior to the corneal scleral limbus.

Following the intravitreal injection, subjects will be monitored for elevation in IOP and for endophthalmitis up to one-hour post-injection. Subjects should be instructed to report any symptoms suggestive of endophthalmitis without delay.

***INTRAVITREAL BROLUCIZUMAB INJECTION PRE-FILLED SYRINGES ARE FOR SINGLE USE ONLY.***

**4.4 Concomitant Therapies**

At the discretion of their physician, subjects may continue to receive all medications and standard treatments administered for other conditions except in the following instances:

* Concurrent use of systemic or intravenous anti-VEGF agents

**4.5 Visit Schedule and Assessments**

\* *See Appendix A for study flowchart.*

Medical and treatment history for all patients will be recorded.

The following evaluations will be performed at ***all*** study visits:

* Vital signs
* Best-corrected visual acuity using ETDRS chart at 4 meters
* Ophthalmic examination including IOP measurement
* SD-OCT

This is a prospective, open-label study. Subjects with treatment resistant active CNV secondary to AMD who meet all inclusion/exclusion criteria will be included in the study. The study will be conducted at 1 site, Sydney Retina, and will recruit approximately 55 subjects.

The Investigator or a designee is responsible for scheduling study visits and ensuring subject compliance with the visit schedule. Subjects missing a scheduled visit should be contacted immediately to reschedule the examination, preferably within the specified study visit period.

SD-OCT imaging, fluorescein angiography (FA) and colour fundus photography will be performed at the Screening Visit and the images will be assessed by PI. ICG will also be performed and the images will be assessed by the PI. The PI will review these images to confirm subject eligibility based upon the lesion attributes specified in the inclusion/exclusion criteria. Subjects who meet all inclusion and exclusion criteria and are confirmed as eligible by the PI will undergo first treatment for the Visit 1/Baseline (Day 0).

**Visits and Examinations**

Details of all procedures, definitions and grading criteria for test parameters can be found in the Manual of Procedures (MOP) for this protocol.

**Study Methods and Measurements**

**VISUAL FUNCTION QUESTIONNAIRE-25**

Quality of life data will be collected with a visual function questionnaire using the National Eye Institute VFQ-25 which is a validated instrument that has been used in many studies of subjects with AMD. The VFQ-25 will be administered by site staff to subjects. The VFQ-25 must be administered before any other examination. The United States English version of the VFQ-25 is included in the MOP.

**BEST-CORRECTED VISUAL ACUITY**

ETDRS visual acuity testing should precede any examination requiring administration of eye drops to dilate the eye or any examination requiring contact with the eye. Visual acuity testing should be performed following refraction and completed according to the procedure outlined in the MOP.

**COMPLETE OPHTHALMIC EXAMINATION**

A complete description of standardized procedures and grading scales is outlined in the MOP. The ophthalmic exam will consist of the following:

* Slit-lamp examination – includes evaluation of the lids/lashes, conjunctiva, cornea, iris, lens, and aqueous reaction (cells and flare).
* IOP measurement – a measurement of intraocular pressure will be conducted using an applanation tonometer.
* Fundus exam – includes evaluation of the vitreous, retina, macula, choroid, and optic nerve. Dilation for the fundus exam is at the discretion of the Investigator.

**SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY IMAGING**

A standardized procedure for the collection of quantitative and qualitative data via SD-OCT is provided in MOP. At the Baseline Visit, retinal images will be reviewed by the PI for determination of eligibility

**FLUORESCEIN ANGIOGRAPHY**

A standardized procedure for the collection of FA images is provided in the MOP. At the Baseline Visit, retinal images will be reviewed by the PI for determination of eligibility. FA images from previous routine evaluations may be used as long as they were performed within 3 days of the Baseline Visit.

**COLOUR FUNDUS PHOTOGRAPHY**

A standardized procedure for the collection of 3-field colour fundus photographic images is provided in the MOP. At the Baseline Visit, retinal images will be reviewed by the PI for determination of eligibility

**INDOCYANINE GREEN**

ICG images will be taken at Screening. A standardized procedure for the collection of ICG images is provided by the MOP. At the Baseline Visit, retinal images will be reviewed by the PI for determination of eligibility

**FUNDUS AUTOFLUORESCENCE**

FAF will be performed in order to assess the occurrence of geographic atrophy. A standardized procedure for the collection of FAF images is provided in MOP. FAF will not be used to determine eligibility but will be included beginning at the Visit 1/Baseline.

**INTRAVITREAL ADMINISTRATION OF INVESTIGATIONAL PRODUCT**

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 nonstudy eyes) prior to every injection. Specific instructions for injection procedures are provided in the MOP.

**POSTINJECTION ASSESSMENT**

The study eye will be assessed before, immediately (0-5 minutes) after and 30 (± 15) minutes after each IVT injection to ensure that the procedure and/or the study medication have not endangered the health of the eye. The post-injection assessments include a gross assessment of vision (eg, count fingers), the status of the central retinal artery, presence of retinal detachment, presence of new intraocular haemorrhage(s), and measurement of IOP according to the schedule detailed in the MOP.

**Assessments will continue until the central retinal artery is adequately perfused and the IOP is within 10 mmHg of the pre-injection value and is stable in the opinion of the Investigator.**

Any subject who develops significantly raised IOP (> 30 mmHg) or a non-adequately perfused central retinal artery at any time during the study should be monitored according to the Investigator’s clinical judgment and may undergo additional procedures and measurements of IOP beyond those specified in the protocol. If, at the conclusion of the required evaluation period following an injection/sham, there are no safety concerns, the subject will leave the site. If any concern or immediate toxicity is noted, the subject will remain at the site and will be treated according to the designated evaluating physician’s clinical judgment. If any issues regarding IOP were noted during the post-injection assessment, then the subject should be scheduled for a follow- up visit (Unscheduled Visit) the day following injection/sham, if required in the opinion of the Investigator. Clinically relevant changes that are observed during the post injection assessment should be reported as adverse events.

**Concomitant Treatment**

The Investigator should instruct the subject to notify the study site about any new medications he/she takes after enrolling into the study.

Should the non-study eye require treatment with an anti-VEGF, this should be applied at the discretion of the Investigator and following the procedures established at the respective site within product information guidelines.

4.6 Early Termination Assessments

Subjects who withdraw from the study prior to completion should return for an early termination evaluation 28 days (± 7 days) following the last injection/study visit for monitoring of all adverse events (serious and non-serious). The schedule of assessments for early termination is the same as that for the final visit.

**4.7 Study Discontinuation**

This study may be terminated by Sydney Retina Clinic or Novartis Australia Ltdat any time. Reasons for terminating the study may include the following:

* The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
* Subject enrolment is unsatisfactory
* Data recording is inaccurate or incomplete

**5 SAFETY**

**5.1 Adverse Events (AEs)**

Information about all AEs, whether volunteered by the subjects, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, must be collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An AE is any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the events not considered being treatment related.

Throughout the course of the study, all efforts will be made to remain alert to possible AEs or untoward findings. The investigator will elicit reports of AEs from the subject at each visit and complete all AE forms. Each AE form is reviewed by the study investigator to verify the coding and the reporting that is required. The study investigator will assess the relationship of any AE to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by study procedures.

Other adverse events requiring reporting include study drug misuse events or study drug abuse events.

### **5.1.1 Definition of Adverse Events**

According to the April 1996 (E6) International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE therefore can be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

If a previously reported AE or pre-existing illness increases in severity or frequency, it will be considered a new event. Any abnormal laboratory value that the Investigator considers clinically significant will be reported as an AE. All AEs determined not to be study drug related will be followed through week 48 and noted as “continuing” if not resolved at the week 48 visit. AEs considered to be study drug related will be followed until they have resolved or stabilizedor, in the case of a pre-existing illness, returned to its baseline status recorded prior to the injection of study drug.

Subjects that are withdrawn from the study due to an AE or experience an AE that is deemed related to the study drug, will be followed until the event has resolved or has stabilized.

### **5.1.2 AE Reporting Requirements**

For each AE the following information will be recorded:

* Name of Event: The Investigator should use standard medical terminology that clearly describes the pathophysiology of the event and identifies the body system affected. If the event is ocular the Investigator should include the eye that is affected;
* Onset Date: Date that the AE was first experienced at the reported severity and frequency;
* Resolution Date: Date that the AE was last experienced or was completely resolved. In the case of an AE that increases in severity or frequency, the resolution of the AE is the date that it was last experienced at that previously reported severity;
* Severity: All AEs will be graded according to the following:
  + Grade 1 = Mild, easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities;
  + Grade 2 =Moderate, sufficiently discomforting to interfere with normal everyday activities;
  + Grade 3 =Severe, prevents normal, everyday activities;
  + Grade 4 =Life threatening, places the patient in immediate risk of death;
* Relationship to Study Drug: All AEs will have a study drug causality assessment performed at the time of reporting the event to document the Investigator’s perception of causality. For the purposes of this clinical study, causality will be assigned using the following criteria:

1. Not Related: A temporal relationship to the investigational product administration, which makes a causal relationship clearly and incontrovertibly due to extraneous causes, such as other drugs, products, chemicals, underlying diseases, environment, etc. Not related to the investigational product.
2. Possibly Related: Occurring within a reasonable period of time relative to the investigational product which makes a causal relationship possible, but plausible explanations may also be provided by other causes, such as other drugs, products, chemicals, underlying disease, environment, etc. Possibly related to the investigational product.
3. Related: The event cannot be attributed to the patient’s underlying medical condition or other concomitant therapy and there is a compelling temporal relationship between the onset of the event and the investigational product administration that leads the Investigator to believe there is evidence of a reasonable causal relationship. Related to the investigational product.
4. Related to Injection Procedure: The event cannot be attributed to the patient’s underlying medical condition or other concomitant therapy and there is a compelling temporal relationship between the onset of the event and the injection procedure that leads the Investigator to believe there is evidence of a reasonable causal relationship.

* Action(s) taken

### **5.1.3 Serious Adverse Events (SAEs)**

The Investigator is required to determine if each AE is an SAE. An SAE is defined as an AE which:

* Results in death,
* Is life-threatening
* Requires inpatient hospitalization or
* Prolongation of existing hospitalization
* Results in persistent or significant disability/incapacity,
* Is a congenital anomaly/birth defect, or
* Requires intervention to prevent permanent impairment or damage

Events not considered to be SAEs are hospitalizations occurring under the following circumstances: were planned before entry into the clinical study; are for elective treatment of a condition unrelated to the studied indication or its treatment; occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the criteria above); are part of the normal treatment of the studied indication and not associated with any deterioration in condition.

### **5.1.4 Serious Adverse Event Reporting Requirements**

All SAEs occurring during the study or within 30 days of the last administration of study drug must be reported to both TGA and Novartis Australia Ltd**.** within 24 hours learning of its occurrence. The principal investigator is responsible for submitting follow-up reports for all SAEs regarding the patient’s subsequent course until the SAE has resolved or until the patient’s condition stabilizes (in the case of persistent impairment), or the patient dies.

### **5.1.5 Follow-up of Adverse Events and Serious Adverse Events**

All AEs determined not to be study drug related will be followed through to week 48, early discontinuation or lost to follow-up will be noted as “continuing” if not resolved at this visit. Any AE that is determined to be study drug related will be followed to resolution or stabilization unless the patient discontinues the study prior to week 48 or is lost to follow-up.

All SAEs, regardless of relationship to study drug, will be followed until resolution or stabilization unless the patient discontinues the study prior to week 48 or is lost to follow-up.

**5.1.6 Reporting Procedures**

The investigator must complete the Serious Event Report Form, assess the relationship to study treatment and submit the form to both TGA and Novartis Australia Ltd. within 24 hours. The original and duplicate copies of the Serious Adverse Event Form, and confirmation sheet to fax must be kept with the case report forms at the study site. Follow-up information is sent to the same person to whom the original Serious Adverse Event From was sent. A new Serious Adverse Event Form is completed, stating that this is a follow-up to previous reported SAE. The follow-up should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation. The form and fax confirmation sheet must be retained.

**5.2 Pregnancy**

Although pregnancy is not considered as an AE, the Investigator should report to Novartis Australia Ltd., immediately, any pregnancy occurring in a female study subject or female partner of a male study subject, either during the study or within 35 days following the last dose of study drug. The Investigator will follow the pregnancy until delivery, and longer if needed. If the pregnancy continues to term (delivery), the health of the infant must also be reported toNovartis Australia Ltd.

### Mandatory early termination from the study is required if a subject becomes pregnant during the study. Pregnant subjects should be informed to immediately discontinue taking injectable study drug

**6. Data Management and Statistical Methods**

Primary analysis data set:

* The primary efficacy analysis data set is the full analysis set (FAS) with missing values imputed by last observation carried forward (LOCF). The FAS includes all subjects who are randomized and received at least one IVT injection. Sensitivity analyses will be performed using the per protocol analysis set (PPS) and alternative imputation for missing values including a mixed model repeated measures (MMRM) and observed data only analyses.

**Statistical testing strategy:**

The 4 hypotheses will be tested in the pre-specified hierarchical sequence according to their numbering (HAn, n=1,2,3,4). Consequently, confirmatory testing of a given hypothesis requires rejection of all preceding null hypotheses. In this setting, each hypothesis will be assessed at a two-sided α = 0.05, while keeping the global type I error rate at 0.05.

**Statistical method:**

Two-sided 95% confidence intervals (CI) for the change in means, based on a paired t-test model with treatment, Baseline BCVA categories (≤ 55, 56-70, ≥71 letters), and age categories (< 75, ≥ 75 years) as fixed effects will be presented for the primary efficacy analysis. The same model will be fitted for the key secondary endpoint, average change in BCVA from Baseline over the period Week 36 through 52.

**Sample size:**

A sample size of 50 subjects is sufficient to demonstrate efficacy of brolucizumab with respect to the BCVA change from Baseline to Week 52 at a two-sided alpha level of 0.05 with a power of approximately 90% assuming equal efficacy and a common standard deviation of 15 letters. A power of at least 90% can be expected for the first key secondary endpoint assuming that averaging over the 4 time points will not lead to an increase in the standard deviation.

To account for a drop-out rate of 10%, a total of 55 subjects will be recruited.

**DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS**

*Completion of Source Documents and Electronic Excel Data Forms*

The nature and location of all source documents will be identified to ensure that original data required to complete the excel spreadsheet exist and are accessible for verification by auditors. If electronic records are maintained, the method of verification must be determined in advance of starting the study. At a minimum, source documents should include the following information for each subject:

Subject identification (name, sex, race/ethnicity) Documentation of subject eligibility Date of informed consent Dates of visits

Documentation that protocol specific procedures were performed Results of study parameters, as required by the protocol Study medication accountability records Documentation of AEs and other safety parameters (if applicable). Records regarding medical histories and the use of concomitant therapies prior to and during the study

Date of study completion and reason for early discontinuation, if applicable

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the excel spreadsheet are consistent with the original source data.

Additionally, the Investigator must keep study records and source documents until the Sponsor provides written approval for their destruction. If the Investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, the Sponsor must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the **latest** marketing approval).

6.1 Safety Analyses

Any adverse events, vital signs, ocular examinations and measurements from all subjects will be utilized to summarize safety data. Reports of adverse events will be reviewed and summarized quarterly and yearly while the study is ongoing to ensure the safety of subjects.

6.2 Efficacy Analyses

Efficacy will be assessed over 52 weeks, by the mean change from baseline in BCVA and central foveal thickness to the values at week 24 and week 52. Descriptive statistics for the change in BCVA, central foveal thickness, macular perimetry, and NEI VFQ-25 from baseline to week 24 and 52 will be presented, along with the corresponding 95% confidence intervals.

In addition to analysis of the total sample population, efficacy analysis will also be performed for stratified groups (visual acuity, lesion characteristics).

6.2.1 Primary Endpoint

* Mean change in PED height at weeks 24 and 52.Proportion of patients with resolution of PED at weeks 24 and 52.

6.2.2 Secondary Endpoints

* Structural changes of PED on OCT-Angiography
* Mean change in visual acuity at weeks 12, 24 and 52 compared to the baseline.
* Proportion of patients who gain 5, 10 and 15 letters at weeks 12, 24 and 52
* Mean change in central foveal thickness and volume measured by SD-OCT at weeks 12, 24 and 52 compared to the baseline.
* Mean change in PED height at weeks 24 and 52 compared to the baseline.
* Proportion of patients with resolution of PED at weeks 24 and 52.
* Mean number of injections over 52 weeks.
* Proportion of patients with development of macular atrophy at week 52.
* The change of retinal function measured by Macular Integrity Assessment (MAIA) at weeks 24 and 52 compared to the baseline.
* Mean change in National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) score between baseline and weeks 24 and 52.

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A: Study Flowchart

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Screen | Day 0  (Baseline) | Wk 1 | Wk 4 | Wk 8 | Wk 12 | Wk 16 | Wk 20 | Wk 24 | Unscheduled Visit/ Early Termination |
|  | -10 – 0 days |  | ±2 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±7 days |
| Informed consent/Medical History/ Demographics/ Study Criteria | X |  |  |  |  |  |  |  |  |  |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X |
| Vital signs | X | X | X | X | X | X | X | X | X | X |
| Pregnancy test if needed | X |  |  |  |  |  |  |  |  |  |
| BCVA | X | X | X | X | X | X | X | X | X | X |
| Ophthalmic examination  Including IOP measurement | X |  | X | X | X | X | X | X | X | X |
| Macular perimeter | X |  |  |  |  |  |  |  | X |  |
| NEI VFQ-25 | X |  |  |  |  |  |  |  | X | X |
| SD-OCT | X |  | X | X | X | X | X | X | X | X (prn) |
| OCT-Angiography |  | X |  |  | X |  | X |  | X |  |
| Colour Photography | X |  |  |  |  | X |  |  | X | X (prn) |
| Fluorescein/ICG angiography | X |  |  |  |  | X |  |  | X | X (prn) |
| Intravitreal brolucizumab |  | Xa,b |  | Xa,b | Xa,b |  | Xb | Xa | Xb |  |
| Adverse events |  |  | X | X | X | X | X | X | X | X |

APPENDIX A: Study Flowchart (contd)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Wk 28 | Wk 32 | Wk 36 | Wk 40 | Wk 44 | Wk 48 | Wk 52 | Unsch Visit/Early Term |
|  | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±3 days | ±7 days |
| Concomitant medications | X | X | X | X | X | X | X | X |
| Vital signs | X | X | X | X | X | X | X | X |
| BCVA | X | X | X | X | X | X | X | X |
| Ophthalmic examination Including IOP measurement | X | X | X | X | X | X | X | X |
| Macular perimeter |  |  |  |  |  |  | X |  |
| NEI VFQ-25 |  |  |  |  |  |  | X |  |
| SD-OCT | X | X | X | X | X | X | X | X (prn) |
| OCT-Angiography |  | X |  | X |  |  | X |  |
| Colour Photography |  |  | X |  |  |  | X | X (prn) |
| Fluorescein/ ICG angiography |  |  |  |  |  |  | X | X (prn) |
| Intravitreal brolucizumab |  | Xa,b |  | Xb | Xa | Xb |  |  |
| Adverse events | X | X | X | X | X | X | X | X |

a – q12w, b – q8w