CLINICAL STUDY PROTOCOL:

Short Title**:** The **br**olucizumab **a**nti-**V**EGF Treatment of **A**MD **S**witch Study (BRAVAS).

Full Title: A twelve month, unmasked, prospective, study evaluating the effectiveness of brolucizumab in subjects with neovascular age-related macular degeneration, resistant to extension of current treatment regimen.

Study Drug	Intravitreal Brolucizumab injection (6.0mg)
Indication studied	Neovascular Age-related Macular degeneration
Protocol Version:	2.0
Date:	18 March 2021
Investigators: Treating physicians: Study Coordinator:	 Dr Nitin Verma (Principal Investigator) Dr Guy Bylsma Dr Andrew Traill Prof Alex Hewitt Dr Beverley Curry

Investigator agreement: I have read the clinical study described in this document. I recognise its confidentiality and agree to conduct the described trial in compliance with Good Clinical Practice and the ethical principles contained in the Declaration of Helsinki and all regulatory requirements.

Principal investigator: Signature Date

Name: Nitin Verma
Address: 182 Argyle St, Hobart. Tasmania 7000

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List of abbreviations

wAMD	Neovascular (wet) age related macular degeneration
AMD	Age-Related Macular Degeneration
BCVA	Best corrected visual acuity
BRAVAS	The **br**olucizumab **a**nti-**V**EGF treatment of **A**MD **s**witch study
CNV	Choroidal neovascularisation
COVID-19	Coronavirus disease 2019
CP	Color fundus photography
CRT	Central Retinal Thickness
CST	Central retinal subfield thickness
CSV	Central subfield volume
ETDRS	Early Treatment Diabetic Retinopathy Study
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IOP	Intra ocular Pressure
IRF	Intra-retinal Fluid
IVT	Intravitreal
LOCF	Last observation carried forward
NEI VFQ	The National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25)
PDT	Photodynamic therapy
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse event
SD-OCT	Spectral Domain optical coherence tomography
SRF	Sub retinal Fluid
TGA	Therapeutic Gods Agency
VA	Visual Acuity
VEGF	Vascular endothelial growth factor
VFQ	VFQ-25 Visual function questionnaire-25
YAG	yttrium-aluminium-garnet

Study Synopsis

Full title	A twelve month, unmasked, prospective, study evaluating the effectiveness of brolucizumab in subjects with neovascular age-related macular degeneration, resistant to extension of current treatment regimen.
Brief title	The **br**olucizumab **a**nti-**V**EGF Treatment of **A**MD **S**witch Study
ALSO known as	BRAVAS
Study sponsor?	Uma Eye Care Pty Ltd /Hobart Eye Surgeons 182 Argyle Street Hobart TAS 7000
Clinical phase	4
Study type	Interventional
Investigational product	Brolucizumab 6 mg/0.05ml
Comparator	None
Objectives	To evaluate the effectiveness of intravitreal brolucizumab in the treatment of CNV secondary to wAMD in patients previously deemed resistant to extension of their regular anti-VEGF (aflibercept, ranibizumab or bevucizumab) treatment interval beyond 4-8 weeks.
Primary objective (s)	To assess the effect of switching to brolucizumab on participant disease activity. • Changes in the proportion of participants with persistent retinal fluid after switching to brolucizumab. • Changes in anatomical outcomes (central retinal thickness (CRT); the central subfield volume (CSV) and/or changes in the height or width of any retinal pigmented epithelium (RPE) detachment between baseline and 48 weeks after switching to brolucizumab
Secondary objectives	To assess the effect of switching to brolucizumab on participants Anti-VEGF regimen: • The proportion of participants with treatment intervals extended beyond baseline frequency • The number of brolucizumab injections over the study period. To assess the effect of switching to brolucizumab on participant best-corrected visual acuity (BCVA). • The proportion of patients maintaining their baseline BCVA • Changes in best-corrected BCVA between baseline and 48 weeks after switching To assess any changes in participant vision-related quality of life (VFQ) between baseline and 48 weeks after switching to brolucizumab To assess the safety and tolerability of brolucizumab
Exploratory objectives	To investigate any association between participant disease status and characteristics at baseline and the study primary and secondary outcomes.
Study population	Subjects ≥ 50 years of age with active choroidal neovascularization (CNV) secondary to age-related macular degeneration (wAMD) currently attending clinic for regular anti-VEGF injections with 8 weeks or less between consecutive treatments in the study eye.

Number of participants	50
Inclusion criteria	1. Males or females ≥50 years 2. CNV secondary to AMD 3. Best corrected baseline visual acuity between 6/6 to 6/60 (85 to 35 letters) on ETDRS chart 4. SD-OCT evidence of IR, SR, Sub RPE fluid or cystoid oedema (but not intra-retinal cysts alone) less than 60 days since last anti-VEGF injection (i.e. not responding to anti VEGF treatment) or who have a recurrence of active disease when treatment intervals are extended. 5. Regular, 4-8 weekly, intravitreal anti-VEGF injections, for a minimum of six months 6. At least one attempt at extending their anti-VEGF treatment regimen.
Exclusion criteria	1. Premenopausal or peri-menopausal women not using contraception 2. Pregnancy or lactation 3. Prior anti-VEGF injection in the study eye within 28 days of baseline 4. Prior treatment with photo dynamic therapy (PDT) within 90 days of baseline and more than 6 prior PDT treatments 5. Significant sub retinal fibrosis, atrophy or other structural change in the retina that might affect the study outcomes. 6. Prior treatment with intravitreal steroid treatment in the study eye within 6 months of baseline 7. Intraocular surgery in the study eye within 2 months of baseline 8. Prior vitrectomy or other surgical intervention for AMD in the study eye 9. Current vitreous haemorrhage or active intraocular inflammation in the study eye 10. Uncontrolled glaucoma in the study eye. Intraocular pressure (IOP) greater than 30mmHg on maximal medical therapy. 11. History of stroke, acute myocardial infarction and transient ischemic attack within 3 months of study enrolment 12. Allergy to fluorescein. 13. Known intolerance to brolucizumab or any of its constituents
Study design	This is an open label study in patients previously treated with intravitreal anti-VEGF (ranibizumab, bevacizumab or aflibercept) for at least six months on a 4 to 8 weekly injection regimen; with at least one failed attempt to extend their treatment interval and who have persistent retinal fluid at their current treatment interval or have recurrent retinal fluid if the treatment interval is extended. Eligible participants will switch their study eye treatment to brolucizumab and have three, monthly, loading doses before commencing a treat and extend regimen where the treatment interval will be extended based on the investigators assessment of disease activity and predetermined criteria normally used in clinical practice.

Study duration	The study will run for 18 months: Six months recruitment with a 12 month treatment period)
Evaluation schedule	Following enrolment participants will be evaluated monthly. At each follow up they will have a clinical ophthalmic examination including intra-ocular pressure measurement, assessment of best corrected visual acuity, macular OCT and fundus photography. A quality of life questionnaire (NEI VQF-25) will be completed at baseline and at study completion. Fluorescein angiography will be performed when clinically indicated.
Ethics and good Clinical Practice	This study will be performed according to principles of Good Clinical Practice (GCP), the declaration of Helsinki, and national laws and regulations about clinical studies. Ethical approval will be obtained from a registered human Ethics Committee (Bellberry). Informed consent will be obtained from all participants prior to enrolment in the study
Clinical trial registration	The study will be registered on the Australian and New Zealand Clinical Trials Registry.
Data monitoring Committee	There will be no formal data monitoring Committee. Participants' response to treatment will be reviewed by the investigators on a case by case basis as they present for review and treatment. Collated statistics on any withdrawal and adverse events will be prepared and reviewed by all investigators at least once a month. Any issues of concern will identified for further discussion and intervention if required. All adverse events which the investigator believes to have a causal association with the study drug will be reported to the drug manufacturer and to the Australian Therapeutics Goods association. *www.tga.gov.au/reporting-problems* All serious adverse events and instances of study drug exposure during pregnancy, study drug misuse or abuse in participants will be reported to the local Novartis Patient Safety team.

1 Introduction.

Neovascular (wet) age related macular degeneration (wAMD) is a macular condition that may lead to rapid onset irreversible central blindness if not treated promptly. The incidence of wAMD increases with age: Smoking, diet, hypertension and hyperlipidaemia are modifiable risk factors which have been identified to increase the risk of developing the disease but variations in 34 genetic loci have also been associated with the disease.[1]

It has only been in the last 15-20 years that the role that vascular endothelial growth factor (VEGF) plays in the wAMD disease process has been identified.[2] VEGFs are a family of polypeptides responsible for vascular development, maintenance and angiogenesis. An inflammatory response to the death of retinal pigmented epithelial cells causes increased levels of VEGF and results in the growth of abnormal, leaky blood, vessels under the retinal pigment epithelium or the adjacent choroid. Leakage of blood and serum from these vessels results in macular oedema, causes tissue damage, and further stimulates the immune response. If untreated, this will ultimately result in scar formation and permanent vision loss. Anti-VEGF treatment inhibits endothelial cell proliferation, prevents the growth of the leaky vessels (neovascularisation), reduces vascular permeability and macular oedema, and prevents further activation of the inflammatory cascade. Intravitreal injection of anti-VEGF has revolutionised the course of the clinical disease and saved the sight of millions of patients with wAMD and other retinal conditions driven by VEGFs.[3] They are currently the gold standard treatment for wAMD.[4]

Currently there are three anti VEGF treatments formulated for intravitreal injection and indicated for treatment of wAMD: ranibizumab; aflibercept and brolucizumab:

- Ranibizumab, a recombinant humanised monoclonal antibody IgG1 monoclonal FAB fragment (48kD) which inhibits all active isoforms of VEGF-A was approved for treatment of wAMD, in 2006, based on data from the ANCHOR and MARINA phase 3 studies.[5,6]

- Aflibercept, a larger recombinant fusion protein consisting of a human VEGF receptor 1 and 2 fused to the Fc region of a human IgG1 (115kD). It acts as a VEGF-A receptor decoy and binds all VEGF-A and VEGF-B isoforms as well as placental growth factors 1 and 2. The VIEW studies reported that compared to ranibizumab, aflibercept exhibited a greater affinity for, and more sustained inhibition of, VEGFs and that the outcomes of participants treated with 2mg aflibercept at 8 weekly intervals did not differ from participants treated with 0.5mg ranibizumab 4 weekly.[7]

- Brolucizumab, is a humanised single chain antibody fragment (scFv) VEGF of 252 amino acids and a mere 26 kDa. Despite being half the size of ranibizumab, brolucizumab binds and inhibits the three major isoforms of VEGF-A (VEGF110, VEGF121, and VEGF165) and blocks VEGFR-1 and VEGFR-2 receptors. As brolucizumab is also a fraction of the size of other anti-VEGFs a greater treatment dose can be provided in the same volume.[8]

Ranibizumab and aflibercept were listed on the Australian PBS for the treatment of wAMD on 1 August 2007 and 1 December 2012 respectively, while brolucizumab is not yet available on PBS.[9,10]

Where the patient's disease characteristics do not meet the strict Australian PBS criteria, bevucizumab, a human monoclonal antibody of 149 KDa that binds all isoforms of VEGF-A is also used off label. Bevucizumab was originally approved for the treatment of colorectal cancer. It has comparable activity and efficacy to ranibizumab[11] but although it has never been licensed for intraocular use it is used widely throughout the world.

When licensed for wAMD treatment the prescribing information for ranibizumab and aflibercept indicated that treatment should be administered every 4-8 weeks (after loading). However, a number of clinical trials, and reports from clinical practice using treat and extend or as required treatment schedules, have demonstrated that some patients are able to have their treatment extended to up to 12 weekly intervals in response to visual and anatomical outcomes.[12,13]

Despite the evidence demonstrating the feasibility of increasing treatment intervals, approximately 30% of patients still require treatment every 4 to 8 weeks to prevent recurrent disease activity and maintain their vision.[14]

The brolucizumab phase 3 clinical trials, HAWK and HARRIER, demonstrated that after loading, a 12 weekly treatment was equivalent to aflibercept every 8 weeks in anti-VEGF naive patients.15 It therefore seems logical to investigate whether the more concentrated dosing available with brolucizumab might be of benefit to patients with residual active disease, and those maintained on anti-VEGF treatment intervals of 8 weeks or less on their current treatment.

Inhibiting active disease and increasing the intervals between injections would reduce the treatment burden on patients, their doctors and their friends/family members. Potentially improving patient compliance and minimising the likelihood of adverse events associated with more frequent injections.

1.1 The aim of the study

To evaluate the efficacy and safety of a treat and extend regimen of intravitreal brolucizumab in patients with CNV secondary to AMD previously deemed to be resistant to regular anti-VEGF treatment interval extension beyond 4-8 weeks.

1.1.1 Primary objective

To assess the effect of switching to, a treat and extend regimen of, intravitreal brolucizumab on participant disease activity.

1.1.2 Primary Outcome measures:

- The proportion of participants with persistent retinal fluid between baseline and 48 weeks after switching to brolucizumab.
- The proportion of participants with retinal fluid in specific locations (Intra-retinal fluid (IRF), sub retinal fluid (SRF) and or as retinal pigmented epithelial (RPE) detachment.
- Changes in anatomical outcomes (central retinal thickness (CRT); the central subfield volume (CSV) and/or changes in the height or width of any RPE detachment between baseline and 48 weeks after switching to brolucizumab

1.1.3 Secondary objectives

1. To assess anti-VEGF treatment frequency after switching to brolucizumab.
2. To assess the effect of switching to brolucizumab on Best Corrected Visual Acuity (BCVA)
3. To assess any changes in patient vision related quality of life (VFQ) that may be directly or indirectly related to switching to brolucizumab treatment.
4. To assess the safety and tolerability of intravitreal brolucizumab 6mg.

1.1.4 Secondary outcome measures:

- The extent of any treatment interval extensions; indicated by the number of injections in the study period.
- The proportion of patients at 48 weeks with treatment intervals extended beyond that at baseline
- The proportion of patients who maintain or improve their BCVA over the course of the study. (Defined as no more than a 5 letter loss or more than a 5 letter gain in BCVA, respectively, between baseline and 48 weeks after switching.)
- Changes in BCVA between baseline and 48 weeks after switching.
- Changes in the health-related quality of life outcomes of NEI VFQ-25 between baseline and 48 weeks.
- Incidence of ocular and non-ocular adverse events over the study period.

2 Study design

This study is a prospective, open label study in patients who have been previously treated with intravitreal anti-VEGF for CNV due to AMD and who, at baseline, have either:

Refractive disease: Persistent active disease (retinal fluid) despite treatment every 4 weeks. OR

Recurrent disease: Stable disease (dry retina) maintained on frequent intravitreal injections (8 weekly intervals or less), with at least one previous attempt at treatment extension, that has resulted in return of recurrent active disease (retinal fluid).

After the subject has been screened and deemed eligible their study eye anti VEGF treatment will be switched to brolucizumab. Their treatment and follow up regimen is presented in Figure 1.

Figure 1: Overview of study design

<table>
<tr><td>Screening</td><td colspan="3">Three monthly loading doses</td><td colspan="4">4 weekly Follow up ←</td><td>Final visit
(no study drug treatment)*</td></tr>
<tr><td rowspan="2">Assessment of eligibility

Week -4 to 0</td><td rowspan="2">Baseline
Week 0</td><td rowspan="2">Week 4</td><td rowspan="2">Week 8</td><td rowspan="2">Week 12</td><td colspan="3">Treatment according to disease activity →</td><td rowspan="2">Week 48</td></tr>
<tr><td>Week
n</td><td>Week
n</td><td>Week
n</td></tr>
<tr><td colspan="9">*If treatment is required at this visit participants may receive brolucizumab (if available in PBS) or another ant –VEGF at the discretion of the investigator</td></tr>
</table>

2.1 Subjects

The study will be conducted in a clinical setting at Hobart Eye Surgeons. Study participants will be identified from the clinic population already attending Hobart Eye Surgeons for treatment or referred to study investigators, by other eye clinics in Hobart, with a view to study participation. Approximately 50 participants will be recruited

At a routine assessment the study will be discussed, and the patient will be provided with a HREC approved participant information document and consent form to read, and discuss with their family and or physician, prior to attending for a screening visit.

2.2 Informed consent procedure

Patients will not be enrolled as participants unless they have provided informed consent. At the screening visit the investigator will discuss the study with the patient to ensure that they understand what study participation entails, what is expected of them, what their rights are as a participant and to answer any questions the patient may have.

On completion of the discussion, and when all of the patient's questions are answered, an HREC approved participant consent form must be signed by the participant, the investigator and an impartial witness if required. The participant will be given a copy of the signed consent form for their records. Written informed consent will be obtained before any study specific measures are done.

Study participation, the consent process and the date of consent will be recorded in the participant's clinic notes, printed and collated in a study file for data entry.

After informed consent, and confirmation of eligibility, all participants will be treated with 6mg/0.05ml intravitreal brolucizumab. Where patients are deemed ineligible they are identified as a 'Screen Failure". The reason for screen failure should be documented in their clinical record.

2.2.1 Inclusion criteria:

- Ability to provide written informed consent and complete study assessments
- Age 50 years or older
- Confirmed diagnosis of CNV secondary to AMD
- Best corrected visual acuity between 6/6 and 6/60 (85-35 letters), on Early Treatment Diabetic Retinopathy (ETDRS) charts, at baseline
- Currently being treated with regular, approximately 4-8 weekly, intravitreal anti-VEGF injections, for a minimum of six months
- At least one attempt at extending their anti-VEGF treatment regimen beyond the current dosing interval
- SD-OCT evidence of IR, SR, sub RPE fluid or cystoid oedema (but not intra-retinal cysts alone) less than 60 days since last anti-VEGF injection (i.e. not responding to anti VEGF treatment) OR who have had a recurrence of IR, SR, sub RPE fluid or cystoid oedema when treatment intervals are extended.

2.2.2 Exclusion Criteria

- Pregnant or nursing (lactating) women
- Pre or peri-menopausal women not using contraception
- Prior anti-VEGF injection in the study eye within 30 days of baseline
- Prior treatment with photo dynamic therapy (PDT) within 90 days of baseline and more than 6 prior PDT treatments
- Significant sub retinal fibrosis, atrophy or other structural change in the retina that might affect the study outcomes.
- Prior treatment with intravitreal steroid treatment in the study eye within 6 months of baseline

- Intraocular surgery in the study eye within 3 months of baseline (excepting cataract surgery)
- Prior vitrectomy or other surgical intervention for AMD in the study eye
- Current vitreous haemorrhage or active intraocular inflammation in the study eye
- Uncontrolled glaucoma in the study eye. Intraocular pressure (IOP) greater than 30mmHg on maximal medical therapy.
- History of stroke, acute myocardial infarction and transient ischemic attack within 3 months of study enrolment
- Allergy to fluorescein.
- Known intolerance to brolucizumab or any of its constituents
- Concurrent use of systemic or intravenous anti-VEGF agents
- Use of any medications known to be toxic to the eye (except for those used short term for the treatment of COVID-19 infection)
- Use of any other unstable medical condition that may potentially affect the study outcomes or the participant's ability to participate in the study.
- Participation in any other clinical trials.

2.3 Study Duration

The study will run for approximately 18 months: 6-month recruitment period and 48 weeks of participant follow up.

2.3.1 Evaluation Schedule:

Following enrolment into this study all patients will be reviewed monthly. Clinical review will include a thorough ophthalmic examination of both eyes, including fundus photography, autofluorescence, measurement of best-correct visual acuity and macular OCT assessment. Fluorescein angiography will be performed when clinically indicated. The NEI-VFQ25 Health related quality of life questionnaire will be administered at baseline and after 48 weeks.

Should a participant have two eyes eligible for inclusion, only one will be included in the study. The investigator will select the study eye as the one with the most potential to respond. Treatment for the fellow eye will continue, as required, throughout the study.

2.3.2 Participant Withdrawal

Participants 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 will be documented in the study database.

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

- Safety concerns
- Non-study intervention for AMD in the study eye
- Pregnancy
- Loss to follow up

- Death

If a participant discontinues from the study, all study data already collected will be retained for analysis; He or she will not re-enter the study and no further efforts will be made to obtain or record additional information unless the participant is pregnant.

If a participant becomes pregnant, permission will be sought to follow the outcome of the pregnancy, and any adverse outcomes will be reported to Novartis.

If a participant becomes lost to follow up three attempts will be made to contact them: Two by phone and one written. If no response is forth coming from these attempts, they will be discontinued from the study.

Should a participant die during the study period, every effort should be made to ascertain the cause of death and report it to the drug manufacturer.

2.4 Study Drug

Brolucizumab, for intravitreal injection, will be supplied by Novartis Australia Ltd in prefilled syringes. All drug supplies are to be kept under the recommended storage conditions.[16] Throughout the study the principal investigator is responsible for ensuring that there is an adequate supply of brolucizumab to treat participants in accordance with the protocol and product information. The study drug may not be used outside the scope of this clinical trial.

The recommended dose of brolucizumab is: "*6 mg in a 0.05 ml solution, administered by intravitreal injection, every 4 weeks (monthly) for the first 3 doses. Thereafter, individualised treatment intervals are permitted based on disease activity as assessed by visual acuity and/or anatomical parameters. In patients without disease activity, treatment up to every 12 weeks (3 months) should be considered.*"

All study participants will receive 6mg/0.05ml intravitreal brolucizumab injection from a prefilled syringe, using aseptic technique and anaesthesia as per local practice.

2.4.1.1 Packaging, labelling and storage

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 co-ordinator), 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 will be opened and stored immediately at the site in a refrigerator intended for investigational products at a temperature of 2° to 8°C. Exposure of the material to temperatures outside these limits, except for warming to room temperature prior to administration, is not recommended and may result in loss of activity.

When prefilled syringes 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/syringe must not be used.

2.4.1.2 *Study* drug accountability

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 and unused study drug syringes will be destroyed at the site or returned to Novartis Australia Ltd or disposed of in sharps bins on site.

The Principal 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, disposed of at the site or returned to Novartis Australia Ltd.

2.4.1.3 Study Drug Administration

The intravitreal injection procedure should be carried out under controlled aseptic conditions in accordance with the manufacturer's directions and routine clinical practice.[16] Appropriate anaesthesia should be given and a broad-spectrum microbicide (chlorhexidine) used to flush the eye prior to injection.

Brolucizumab pre-filled syringes are for single use only. The volume contained in the pre-filled syringes is 0.165 ml. This is more than twice the recommended dose of 0.05 ml. If the entire volume of the pre-filled syringe was injected this could result in overdose. A portion of the volume contained in the pre filled syringe must therefore be discarded prior to administration.

As per the product information, the air bubble and excess medicinal product should be removed from the syringe as follows: The plunger should be slowly depressed until the edge below the dome of the rubber stopper is aligned with the 0.05 ml dose mark (equivalent to 6 mg brolucizumab).

The study drug will be given by intravitreal injection 3.5 to 4mm posterior to the corneal scleral limbus.

Following the intravitreal injection, participants should be monitored for elevation in IOP and for endophthalmitis. Subjects should be instructed to report any symptoms suggestive of inflammation or endophthalmitis without delay.

2.4.2 Study intervention

After informed consent, and confirmation of eligibility at a screening visit, all participants will be treated with three (loading) doses of 6mg/0.05ml intravitreal brolucizumab at day 0, week 4 and week 8. Thereafter (at 12 weeks and beyond) participants will be treated according to a treat and extend regimen where the treatment interval will be extended based on the investigators assessment of active disease activity based on predetermined criteria normally used in clinical practice:

- the presence of IR, SR or Sub RPE fluid on OCT or
- evidence of any new retinal haemorrhage and/or
- a reduction in vision (BCVA) of 5 letters or more (deemed attributable to wAMD) since commencing the study.

A participant's treatment interval may be extended by two weeks if none of the above criteria are met. If previously extended the treatment interval may be reduced by two, or four, weeks based on the presence of one or more signs of active disease. The minimum interval between treatments will be 4 weeks. The longest interval between treatments will be 12 weeks.

2.4.3 Concomitant medications

At screening, all current medications and those taken in the 90 days prior will be recorded. Any changes or additions to the participant's medications, and non-drug therapies, over the study period will also be documented to ensure that no contra-indicated treatments are being taken.

Systemic anti-VEGF treatment is not permitted but a fellow eye that already has wAMD, or develops wAMD during the course of the study, may be treated with intravitreal anti-VEGF as required. The fellow eye will be monitored at the discretion of the investigator.

Topical corticosteroids are allowed, but intra-ocular steroids or systemic steroids are permitted unless the latter are used short term for the treatment of COVID 19 infection.

Post cataract, Yttrium garnet (YAG), laser is permitted if required but should preferentially be performed prior to study participation. Focal or grid laser in the study eye is not permitted at any time during the study.

2.5 Study methods and data collection measurements

2.5.1 Visit Schedule and Assessments/Procedures

An overview of the study design is presented in Figure 1 and a schedule of the assessments that will be conducted at each visit is presented in **Error! Reference source not found.** on page 22.

The participant will attend a screening visit to determine eligibility.

Eligible participants will switch their study eye treatment to brolucizumab and have three, monthly, loading doses before commencing the treat and extend regimen.

2.5.1.1 Screening/Baseline

Table 1 lists the information that will be collected from participants at their screening/baseline visit.

Table 1: Baseline data collection

Demographic data	Patient assessments and baseline data
Age Sex Current medications and medical history Smoking status: Current/Past/Never Smoker cigs/day Study eye Date of AMD diagnosis Current treatment Current treatment interval How long CTI? Previous treatments (Single/ Prev switch) Fellow eye status wAMD/AMD/healthy Fellow eye diagnosos date Fellow eye treatment (if relevant) Previous treatments (Laser treatments)	Height Weight Vital signs (Blood pressure and pulse) Pregnancy test (if indicated) National Eye Institute NEI VFQ-25 validated instrument to assess vision related quality of life[17] Uncorrected Distance VA (Both eyes) Best corrected Visual acuity at 4m after subjective refraction (Both eyes) Intra-ocular pressure (Both eyes) SD-OCT: characteristics and location of macular oedema. [IRF/SRF/ Sub RPE; the CRT and CRV (at 1 and 6mm of the fovea) and the height and width of any RPE detachment if applicable]. Slit lamp and dilated fundus examination both eyes to ensure that there are no contra-indications to injection (in particular, any signs of infection or inflammation)

Participants will be reviewed every 4 weeks after their first injection at which the following study assessments will be collected:

- Patient questionnaire: The impact of switching to brolucizumab on subject visual function will also be assessed by a visual function questionnaire, the National Eye Institute NEI VFQ-25 which is a validated instrument that has been used in many studies of patients with macular degeneration.[17,18]

2.5.1.2 Follow up

Efficacy

- SD-OCT macular examination will be conducted using the Heidelberg "Spectralis" HRA and OCT. The images will be obtained by a trained technician and the same OCT machine and the "follow up function" will be used for follow up measures at each visit. The SD-OCT imaging will be performed after assessment of BCVA and before any treatment and will be used to assess the participant's response to treatment.

  The central retinal thickness (CRT) the average thickness of the area of the macular within 1mm and 6mm of the fovea will be measured by the OCT.

- Best Corrected Visual acuity will be assessed using an EDTRS chart at 4 metres using the best correction obtained after subjective refraction. The refraction will be performed, by a trained technician, in the study eye at all study review visits and in the fellow eye at screening and week 48.

At week 12, and thereafter, the investigator will use the results of the above examinations to determine the time to the participant's next injection as the criteria used to determine extension of treatment interval are:

- The absence of any macular oedema (excluding small cysts)
- BCVA stable, improved or reduced by <5 compared to baseline

2.5.1.3 Safety

Safety checks are performed before and after the study treatment at each visit. This will ensure that there are no contra-indications to injection and ensure that there are no adverse events associated with the drug injection. Intra-ocular pressure (IOP) is measured before and after injection. Any elevation in IOP that persists more than 30 minutes post injection will be treated as per investigator. Such participants will not leave the clinic until their IOP has returned to normal.

Table 2: Safety assessments

Assessments prior to study treatment	Assessments after study treatment
Question participant to establish whether there have been any changes in participant's health or medications since baseline their last visit Vital signs Intraocular pressure (using iCare) Slit lamp and dilated fundus examination study eye (or both eyes at the discretion of the investigator)	Perform a post injection check within 5 minutes of injection Record patients IOP in study eye within 60 minutes of injection Evaluation of any other adverse events or additional medications required post injection

2.5.1.4 Additional safety measures

Should the participant exhibit any signs of intraocular inflammation, at any time during the study, additional OCT, colour fundus photography and fluorescein angiography will be performed to further evaluate the issue.

2.5.2 Injection only visits outside the 4 week follow up cycle

The injection interval will increase by two weeks if the participant shows no signs of active disease in the study eye. If the study injection frequency does not coincide with a 4 weekly visit, the participant must have the following:

A thorough ophthalmic exam (slit lamp and dilated fundus examination) of the study eye pre-injection to ensure that there are no contra-indications to injection (in particular, any signs of infection or inflammation)

Post injection checks vision and IOP (within 5 and 60 minutes of injection respectively) will also be conducted to check for adverse events.

2.5.3 Final visit

Participants competing the study at 48 weeks (+/- 1 week) and, where possible, those withdrawing from the study prematurely for any reason will complete a self administered NEI VFQ 25 in addition to the routine efficacy assessments indicated above. Further assessments (fundus photographs and fluorescein angiograms) may be required if deemed necessary by the investigator if for example the participant is withdrawing because of an ocular adverse event.

2.5.4 Missed visits

Missed visits due to illness, including COVID 19, do not necessarily result in discontinuation. Participants should attend for assessment and treatment, as soon as they are available, prior to any decision about discontinuation.

2.5.5 Early Termination Assessments

The study treatment period is 48 weeks. If study treatment is discontinued prior to 48 weeks the participant should, where possible, continue to attend for review in accordance with the study protocol.

As indicated above, participants who withdraw consent to participate prior to completion will be offered an early termination evaluation 28 days (±7 days) following the last injection visit to monitoring for any adverse events. The schedule of assessments for early termination is as per a final visit.

2.5.6 Loss to follow up

In the event that a participant does not attend for their study appointment, and is not contactable, a reasonable attempt should be made to re-contact them by telephone and in writing. Such attempts should be documented in the participant's case notes.

2.5.7 Study Discontinuation

This study may be terminated by Hobart Eye Surgeons or Novartis Australia Ltd at any time. Reasons for terminating the study may include the following:

- The incidence or severity of adverse events in this or other studies of brolucizumab indicate a potential health hazard to participants
- Subject enrolment is unsatisfactory

2.5.8 End of participation

When the study concludes, is terminated, or a participant withdraws from the study, administration of brolucizumab by study investigators will cease. This will not preclude the participant from receiving intravitreal injection treatment for wAMD outside the study. Participants will be encouraged to consult with their medical practitioner to discuss an available treatment regime that is appropriate for their needs.

3 Safety

3.1 Adverse Events

According to the April 1996 (E6) International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), an adverse event (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, regardless of whether or not it is related to the medicinal (investigational) product. In addition, if a previously reported AE or pre-existing illness increases in severity or frequency, it will be considered a new event. All adverse events occurring over the course of the study will be recorded in the patient file and summarised for review by the investigators and Novartis Australia Ltd and for publication.

All adverse events where the investigator believes there may be a causal association with the study drug (adverse drug reactions (ADE)) will be reported to the drug manufacturer and to the Australian Therapeutics Goods association at: *www.tga.gov.au/reporting-problems*. Subjects that are withdrawn from the study due to an AE or ADE will be followed until the event has resolved or the condition has stabilised.

3.2 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.

3.3 Serious Adverse Event Reporting Requirements

All SAEs occurring during the study must be reported to Novartis Australia Ltd**.** within 24 hours learning of its occurrence. The investigator is also 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 stabilises (in the case of persistent impairment), or the patient dies.

Adverse event monitoring should be continued for 30 days after last administration of study treatment.

3.4 Pregnancy

All women of child bearing potential will be advised of the importance of using contraceptives during the study. They will have a pregnancy test at screening and prior to every brolucizumab treatment, if eligible to participate

Although pregnancy is not considered as an adverse event, 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.

3.5 Harm minimisation

In order to minimise harm, only patients meeting the study inclusion/exclusion criteria (and prescribing restrictions in the brolucizumab prescribing information) will be accepted as participants in the study. Women and male partners of women of child-bearing potential will be cautioned about the potential risks of anti-VEGFs to the foetus and the importance of adequate contraceptive methods.

The risks to the participant are those associated with routine clinical appointments and intravitreal injection. Brolucizumab will be administered in accordance with its indication. All investigators have Medical Indemnity that covers them for any untoward outcomes associated with their clinical work.

4 Data Management and Statistical Methods

This is a hypothesis generating study investigating whether switching to brolucizumab will enable patients currently requiring anti-VEGF treatment at 8 weekly intervals or less to have their treatment interval extended. There is no formal sample size calculation for this study. The sample size is an estimate of the patients that might be recruited from clinic over the designated recruitment period after reviewing the number of patients currently attending clinic who are being maintained on a 4-8 weekly anti-VEGF regimen.

A sample size of 50 subjects is chosen, to ensure that it is feasible to complete the study within 18 months (from the time of enrolment of the first patient to study completion by the last patient.

However, assuming 30% of participants have retinal fluid at baseline also have retinal fluid at 48 weeks using our sample size of 50 participants we would expect the true rate to be between 23.5% and 42.7%.

4.1 Analysis of Data

The analysis will include descriptive statistics such: the number, mean, standard deviations, median, range and confidence intervals for continuous variables and the frequencies and proportions of categorical variables.
Mean changes in continuous variables will be determined using paired t-tests. The presence of confounding may also be evaluated in regression models by including baseline covariates such as: the patient age, smoking status, disease status, duration of current treatment and study eye baseline visual acuity

Missing outcome measures values will be imputed by the last observation carried forward (LOCF) as the primary approach.

4.1.1 Analysis set:

a) Intention to treat. Those consented and eligible who received at least 1 injection

b) As per protocol.

a and *b* will be stratified according to participant disease status (refractive or recurrent) at baseline; and BCVA at baseline (≤55 vs. >55 letters).

c) An internal comparison of outcomes, in the fellow and study eyes, of participants who had two eyes eligible at baseline, where the fellow eye treatment (the drug used and the treatment interval) remained unchanged for the duration of the study will be conducted if feasible.

4.1.1.1 Descriptive demographics

Age, sex, study eye, fellow eye treatment, duration of previous treatment, previous switches, baseline treatment interval and site of ME, Medical history and medications

4.1.1.2 Primary Efficacy Endpoint

- Proportion of participant eyes which are dry, (no IR, SR or Sub RPE fluid) at 48 weeks. Stratified according to baseline disease status and treatment frequency.
- Mean change in Central subfield thickness (CSFT) and Central subfield volume (CSV) measured by SD-OCT overall, and according to baseline disease status and treatment frequency.

4.1.1.3 Secondary Efficacy Endpoint

- Proportion of patients, at 48 week, with treatment intervals extended beyond that of baseline.
- Mean difference in treatment intervals at 48 weeks compared to baseline
- Mean number of injections between week 8 and 48 week (10 maximum, 4 minimum)
- Proportion of patients at 48 weeks, who maintain their vision (BCVA), defined as a < 5 letter loss overall according to whether treatment intervals are extended beyond that of baseline.
- Mean change in visual acuity at 48 weeks overall, and according to whether treatment intervals are extended beyond that of baseline.
- Proportion of patients with new haemorrhages at weeks 24 and 48.

4.1.1.4 Other Secondary Endpoints

Mean change in Health related Quality of Life scale using NEI VFQ- 25 total score between baseline and week 48.

4.1.1.5 Safety endpoints

The number of adverse events by system order class between consent and week 48.

5 Ethical considerations

This study will be performed according to principles of Good Clinical Practice (GCP) E6 (R2) the declaration of Helsinki, and National Health and Medical Research Council guidelines and will comply with Australian and Tasmanian laws and Privacy Principles on clinical trials.

The protocol and participant information letter and consent form (PICF) will be submitted to a registered human Ethics Committee (Bellberry Ltd) for ethical review and approval. The participant's treating ophthalmologist will obtain informed consent prior to their enrolment in the study.

Any amendments to the protocol and/or PICF will also be submitted for review and revised documentation will not be implemented until approval is obtained.

5.1 Confidentiality

After informed consent at screening, participants will be allocated a study number. With the exception of BCVA data assessment records, study data will be entered on patient electronic record as per their regular visits. Data from the electronic record and paper print outs will be transcribed into a study specific, password protected, de-identified, study database on the Hobart Eye Surgeons clinic server. The original copies of signed patient consent forms and a printed copy of the source data will be printed and stored in a locked cabinet so that it is available for data validation by the study team or external authorities (HREC or TGA).

The data in the database will be de-identified (will not contain participant names or addresses or dates of birth) but within the clinic this data will be re-identifiable, as the participant's study participation and screening number will be recorded in their clinical notes. Regardless of the medium (print or presentation) reports documenting study outcomes will be presented as summary data. Individual participants will not be identified.

5.2 Access to data

Only those directly involved in the participants' care or investigators in the study will have access to the study data However, members of the Bellberry Human Research Ethics Committee (that approved this study) and the Therapeutic Goods Administration Australia (TGA), the government agency responsible for regulating and monitoring the use and safety of medications used in Australia, may also inspect the study records to ensure that the study has been conducted according to the approved protocol.

All study documentation and participant records containing data transcribed to the study database will be retained, stored securely, and be made available for inspection by the HREC or TGA for 15 years after study completion

5.3 Declaration of interest

The investigators have no a financial interest in outcomes of this study and have no financial links to the manufacturer of the study drug. The study is being conducted solely with a view to improving the outcomes for patients.

Novartis Australia Ltd have agreed to provide the study drug and will also provide some compensation for study measures, that would not normally be conducted at all, or as regularly in routine care, so that neither the patient or Medicare are out of pocket. They will also provide access to statistical services, at our request, but will have no role in interpreting or reporting the results.

5.4 Dissemination policy

The results of the study will be presented at scientific/medical conferences and will be published in an ophthalmology journal.

Participants' individual results will be discussed with them throughout the study as they attend for their follow up visits. A lay summary of the study results will be provided to them on completion of the final manuscript.

All listed investigators have been invited to review and will contribute to this protocol and to any poster, presentation or manuscript of interim or final results.

De-identified data and statistical analysis code may also be made available for other, ethically approved research, on request.

5.5 Data monitoring Committee

There will be no formal data monitoring Committee. Participants will be reviewed by the investigators on a case by case basis as they present. Collated statistics on any withdrawal or adverse events will be prepared for review for all investigators at least once a month and feedback on the report will be sought. An investigator meeting will be held to discuss any adverse event signals of concern and what action should be taken. All adverse events which the investigator believes to have a causal association with the study drug will be reported to the drug manufacturer and to the Australian Therapeutics Goods association. *www.tga.gov.au/reporting-problems*.

All serious adverse events and instances of study drug exposure during pregnancy, study drug misuse or abuse in participants will also be reported to the study drug manufacturer within 24 hours of the investigator becoming aware of the event.

Table 3: Schedule of Assessments and events over the course of the study

	Screening	Day 0*	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
	-10 to 0 days	Day 0	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days	±7 days
Informed consent	X													
Medical History/ Demographics	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test if pre or perimenopausal	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP	X$	X$	X	X	X	X	X	X	X	X	X	X	X	X$
BCVA	X$	X$	X	X	X	X	X	X	X	X	X	X	X	X$
NEI VFQ-25	X													X$
SD-OCT	X$	X$	X	X	X	X	X	X	X	X	X	X	X	X$
Color Photography	X$		X	X	X	X	X	X	X	X	X	X	X	X$
Fluorescein angiography#	X$													X$
Ophthalmic examination**	X$	X$	X	X	X	X	X	X	X	X	X	X	X	X$
Inclusion/Exclusion Criteria	X	X												
Intravitreal brolucizumab**		X	X	X	X	X	X	X	X	X	X	X	X	
IOP post injection**		X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X

IOP, intra-ocular pressure; BCVA, best corrected visual acuity; NEI VFQ-25, National Eye Institute Visual Function Questionnaire 25; SD-OCT, spectral-domain optical coherence tomography; $Assessments of both eyes. *Day 0 may be combined with the screening visit; **Includes a thorough examination to check for any signs of inflammation; *** From week 12 the administration interval may be extended by two weeks per visit at discretion of the Investigator based on clinical assessment. In some instances the scheduled study injection may fall out with the 4 weekly review date. If this is the case a thorough ophthalmic exam should be performed pre-injection. The minimum treatment interval will be 28 days. # Conducted at these time points (and at any other time) if deemed necessary by investigator.

6 References

1. Paul Mitchell, G. L. B. G. a. T. Y., 2018. Age-related macular degeneration. Lancet, 29 September, Volume 392, pp. 1147-1159.

2. Aiello LP, Avery RL, Arrigg PG et al. Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders. N. Engl. J. Med.1994; 131:1480–1487

3. Papadopoulos P, Martin J, Ruan Q et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab Angiogenesis 2012; 15:171-185. DOI 10.1007/s10456-011-9249-6

4. Papadopoulos Z Recent Developments in the Treatment of Wet Age-related Macular Degeneration Current Medical Science 2020 40(5):1-7

5. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY; MARINA Study Group: Ranibizumab for neovascular agerelated macular degeneration. N Engl J Med 2006, 355:1419 –1431

6. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S; ANCHOR Study Group: Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006, 355:1432–1444

7. Heier JS, Brown DM, Chong V, et al; VIEW I and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. HYPERLINK "http://www.ncbi.nlm.nih.gov/pubmed/23084240" \o "Ophthalmology." Ophthalmology. 2012;119:2537–2548.

8. Nguyen, QD, Das A, Do DV, Dugel PU Gomes A et al. Broluciiiizumab: Evolution through preclinical and clinical studies and implications for the management of neovascular age related macular degeneration. Ophthalmology 2020 127(7) 963-976

9. Department of Health, Pharmaceutical Benefits scheme Public Release Document, May 2018 Drug utilisation sub-committee (DUSC) Meeting. Ranibizumab and aflibercept: analysis of use for AMD, DMO, BRVO and CRVO. https://www.pbs.gov.au/industry/listing/participants/public-release-docs/2018-05/aflibercept-ranibizumab-DUSC-PRD-2018-05.pdf

10. Department of Health, Pharmaceutical Benefits scheme Public Release Document July 2020 Brolucizumab: Solution for intravitreal injection 19.8 mg in 0.165 mL pre-filled syringe; Beovu® https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2020-07/brolucizumab-solution-for-intravitreal-injection-19-8-mg

11. CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ: Ranibizumab and bevacizumab for neovascular age related macular degeneration. N Engl J Med 2011, 364:1897–1908

12. Optimising the Anti-VEGF Treatment Strategy for Neovascular Age-Related Macular Degeneration: From Clinical trials to real life requirements. Mantel I. Trans Vis SCi Tech 2015;4(3):6/tvst.4.3.6

13. Arnold JJ, Campain A, Barthelmes D, Simpson JM, Guymer RH, et al. Fight Retinal Blindness Study Group. Two-year outcomes of "treat and extend" intravitreal therapy for neovascular age-related macular degeneration. Ophthalmology. 2015; 122(6):1212-9. doi: 10.1016/j.ophtha.2015.02.009.

14. Treat and Extend Treatment Interval Patterns with Anti-VEGF Therapy in nAMD Patients. Skelly A, Bezlyak V, Liew G, Kap E and Sagkriotis A.Vision 2019, 3, 41; doi:10.3390/vision3030041

15. Dugel PU, Koh A, Ogura Y, Jaffe GJ Schmidt-Erfurth U et al. HAWK and HARRIER: Phase 3, Multicenter, Randomized, Double-Masked Trials of Brolucizumab for Neovascular Age-Related Macular Degeneration. https://www-ncbi-nlm-nih-gov.ezproxy1.library.usyd.edu.au/pubmed/30986442 Ophthalmology 2020;127:72-84

16. Australian Product Information – Beovu® (Brolucizumab) Solution For Injection. https://www.tga.gov.au/sites/default/files/auspar-brolucizumab-rbe-200414-pi.pdf

17. Revicki DA, Rentz AM, Harnam N, Thomas VS, Lanzetta P. Reliability and validity of the National Eye Institute Visual Function Questionnaire-25 in patients with age-related macular degeneration. Invest Ophthalmol Vis Sci. 2010 Feb; 51(2):712-7. doi: 10.1167/iovs.09-3766. Epub 2009 Sep 24. PMID: 19797233

18. Taylor DJ, Hobby AE,Binns AM, et al How does age-related macular degeneration affect real-world visual ability and quality of life? A systematic review BMJ Open 2016;6: e011504 doi:10.1136/bmjopen-2016-011504

7 Appendices

Appendix 1: Beovu Australian Government. Department of Health . Therapeutic Goods Administration Medicines Registration. Decision summary. 24 January 2020 https://www.tga.gov.au/apm-summary/beovu

Appendix 2:BEOVU® solution for injection brolucizumab (rbe) Consumer Medicine Information. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2020-CMI-01087-1&d=202102161016933

Appendix 3: Hobart Eye Surgeons Study injection protocol

Appendix 4: BRAVAS Participant information and consent form