**PARTICIPANT INFORMATION SHEET AND CONSENT FORM**

|  |  |
| --- | --- |
| **Study Title** | Brolucizumab Treatment for Pigment Epithelial Detachment in Treatment-Resistant Neovascular Age-Related Macular Degeneration. |
| **Protocol Number** | CRTH258AAU04T |
| **Principal Investigator** | Associate Professor Andrew Chang |
| **Sub-Investigators** | Dr James Wong, Dr Thomas Pham, Dr Yasser Tariq |
| **Location** | Sydney Retina, 13/187 Macquarie Street, Sydney, NSW, 2000 |

**Part 1 What does my participation involve?**

1. **Introduction**

You are invited to take part in a clinical research project. This is because you have an eye disease called neovascular Age-related Macular Degeneration (wet AMD). The study is determining the effectiveness of a new treatment for patients with exudative age-related macular degeneration (AMD) and pigment epithelial detachments who have shown poor response to previous anti-VEGF treatments. The drug is called brolucizumab and will be administered as an injection into the eye; an intravitreal injection.

This participant information form will help you to understand the possible risks and benefits involved in the study. In addition, your rights and responsibilities will be outlined. Please note you cannot receive any reward for being a part of this study.

Please read this information carefully. Ask questions about anything that you don’t understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor. Participation in this research is voluntary. If you do not wish to take part, you don’t have to. You will receive the best possible care whether or not you take part. If you decide you want to take part in the research project, you will be asked to sign the consent section.

By signing it you are telling us that you:

* Understand what you have read.
* Consent to take part in the research project.
* Consent to have the tests and treatments that are described.
* Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

1. **What is the purpose of the study?**

As previously stated, you are invited to participate in a research study, which is being conducted to evaluate the effectiveness of intravitreal brolucizumab in the treatment of patients with pigment epithelial detachments secondary to wet AMD who have shown poor response to previous anti-VEGF treatment over 12 months.

The standard treatment for wet AMD involves an injection into the eye which affects the blood vessels in the retina. This involves a medication known as an anti-vascular endothelial growth factor (anti VEGF) such as Eylea (Aflibercept), which is approved in Australia, United States, Japan, and Europe.

Brolucizumab has been approved by the Australian Register of Therapeutics Goods (ARTG) for the treatment for wet AMD in Australia. It has a similar action to ranibizumab (Lucentis) but has a smaller molecular size. Previous studies with brolucizumab have shown that it is as effective as ranibizumab and aflibercept (Eylea) in improving visual outcomes whilst requiring less treatments.

As part of the study, you will receive injections monthly for the first 3 injections. After this initial loading phase, injections will occur every 8 week or 12 weeks until week 52 of the study based on disease activity assessments.

1. **Who will take part in this study?**

AMD patients who have been previously treated with intravitreal Eylea, Lucentis or Avastin who are show persisting pigment epithelial detachment of the macula despite regular injections, will be invited to participate. The study will be performed at Sydney Retina and you will be followed up for a period of 12 months.

You will not be eligible to participate in this study if you are pregnant, planning to become pregnant or are breastfeeding. We will conduct a urinary pregnancy test prior to commencing the study to check this if needed. Any participants of child-bearing age will be requested to use adequate birth control methods during the study.

Patients with both eyes affected will receive the study treatment in one eye only. The other eye will receive care as directed by your doctor.

1. **Study procedures**

You may be invited to participate if you meet the study requirements. We will also ask you to sign the attached participant consent form if you choose to participate in the study. If you choose not to participate in the study, you may continue to receive the same treatment and assessment schedule as you are currently.

This study will run for 12 months. All participants will initially receive intravitreal brolucizumab injection at monthly intervals for the first 3 injections, followed by either 3 or 5 injections for the next 10 months.

Screening visit

At your first visit, the following procedures will be performed to determine whether you are suitable for participation in the study. These include:

* You will be required to sign this informed consent form.
* Your ocular and systemic medical history will be reviewed.
* The study entry criteria, which you must meet to join this study, will be reviewed.
* Demographic information including height and weight will be collected.
* Review of any prior or current ocular and systemic medications that you are currently taking or have recently taken will be recorded.
* Vital signs including body temperature, blood pressure and a heart rate measurement will be taken.
* Visual acuity testing will be performed. You will be asked to read letters on an eye chart to see how well you can see in both eyes.
* Intraocular pressure (IOP) of your eyes will be measured by a device called a tonometer to determine the pressure within your eye. Before the test, an anaesthetic drop will be placed in your eye.
* A slit lamp examination will be performed to check for inflammation or swelling on the surface of your eyes or within your eyes.
* A dilated fundoscopy will be performed to examine the back of your eye. Eye drops will be instilled to make your pupils larger.
* Optical coherence tomography (OCT) and optical coherence tomography-angiography (OCT-A) will be performed. These are non-invasive, non-contact imaging technique that can provide the information about the macula.
* Colour fundus photography will be taken. This involved a photograph of the rear of the eye known as the fundus.
* Fluorescein angiogram (FA) and indocyanine green angiogram (ICGA) will be performed. These involve injecting two kinds of dyes into a vein in your arm and taking photographs of the back of your eye. Each dye provides us with different information regarding the circulation to the eye and allows us to diagnose the type of lesion occurring in your retina more accurately. The entire test will take about 30 minutes in total.
* Macular integrity assessment microperimetry: A test involving looking for a light that is projected over different retinal locations, which provides us the function information of your retina.
* A questionnaire regarding your vision, your general health, and the quality of life.

The screening visit will take 2 to 3 hours.

If you are eligible for the study, you will receive an intravitreal brolucizumab injection at the first visit.

Week 1 to Week 8

All participants will initially receive intravitreal brolucizumab injection at monthly intervals for 3 months. Over the first 3-month follow-up period, you will need to visit the study clinic 7 days after the first injection and then return monthly. At each visit, your visual acuity and eye will be examined, and the macular fluid will be assessed by OCT scan.

Each visit will take 1 to 3 hours.

Week 1 after first injection

The following examinations will occur:

* Visual acuity: You will be being asked to read letters off a chart to see how well you can see out of both eyes.
* Intraocular pressure: The pressure in your eyes will be measured at each visit by a device called a tonometer. Before the test, an anaesthetic drop will be placed in your eye.
* A complete eye examination: Your eyes will be examined by slit lamp biomicroscope after pupil dilation.
* Optical coherence tomography (OCT): This is a non-invasive, non-contact imaging technique that can provide the information about the macula.
* Examination and questioning to exclude adverse events.

Week 4 The following examinations will occur:

* Visual acuity: You will be asked to read letters off a chart to see how well you can see out of both eyes. Intraocular pressure: The pressure in your eyes will be measured at each visit by a device called a tonometer. Before the test, an anaesthetic drop will be placed in your eye.
* A complete eye examination: Your eyes will be examined by slit-lamp biomicroscope after pupil dilation.
* Optical coherence tomography (OCT): This is a non-invasive, non-contact imaging technique that can provide the information about the macula.
* Examination and questioning to exclude adverse events.
* If no adverse events are identified, you will receive the second intravitreal injection of brolucizumab injection.

Week 8 The following examinations will occur:

* Visual acuity: You will be asked to read letters off a chart to see how well you can see out of both eyes.
* Intraocular pressure: The pressure in your eyes will be measured at each visit by a device called a tonometer. Before the test, an anaesthetic drop will be placed in your eye.
* A complete eye examination: Your eyes will be examined by slit-lamp biomicroscope after pupil dilation.
* Optical coherence tomography (OCT) and optical coherence tomography-angiography (OCT-A): These are non-invasive, non-contact imaging technique that can provide the information about the macula.
* Examination and questioning to exclude adverse events.
* If no adverse events are identified, you will receive the third intravitreal injection of brolucizumab injection.

Next 9 month follow-Up

 You will need to visit our clinic monthly to monitor your response to the treatment and you will receive intravitreal Brolucizumab at two monthly intervals.

At each visit, visual acuity, eye examination and OCT scans will be done. At month 6 and month 12, you will also have examinations of FA, fundus photo, flicker frequency perimetry and complete a questionnaire.

Participation in this study may reveal that you have an impairment that is likely to affect your ability to control a motor vehicle. If you have a driver's licence, the law in NSW requires the holder of a driver licence to notify, as soon as practicable, the Roads and Maritime Services (RMS) of any long term injury or illness that may impair your ability to drive safely. Your study doctor will discuss support services if required.

Intravitreal injection procedure

Injections with Brolucizumab will be conducted in a manner almost identical to the Lucentis or Eylea injections you have been receiving. This involves lying in a chair located in a sterile room. Anaesthetic eyedrops are placed into your eye and your eye will be cleaned with an antiseptic solution. Brolucizumab will then be injected into the eye. You may feel slight pressure, but you should not feel pain. The treatment will take around 10 minutes.

**5. Risks and discomforts**

There are risks associated with all medical procedures. Some risks may not be known at present but could also occur. In the event of any problem developing, you will receive suitable medical care and it may be necessary for you to cease receiving the study medication.

Risk of angiography

Both FA and ICGA are safe tests which are routinely used in diagnosis of retinal conditions in clinics. For this procedure, we will need to place a needle into a vein in your arm, which may cause you some discomfort and can result in bruising at the site where we place the needle.

These dyes may stain your skin and urine for some hours after the injection. There is also a small risk of an allergic reaction to these dyes. The most common reactions are nausea, vomiting, or dizziness; however, in rare cases the reaction can be very serious, and may cause difficulty in breathing or even death.

Risk of intravitreal injection

Intravitreal injection of drugs (including Brolucizumab) into the eye is a very safe procedure for the treatment of eye diseases. Despite this, there are still some discomforts and risks associated with the procedure. These include:

* Irritation or redness of the eye, bleeding under the white portion of the eye (subconjunctival haemorrhage) or floaters in your vision. These symptoms are usually temporary and will resolve over a few days.
* Increased intraocular pressure and inflammation.
* More serious side effects include cataract formation, bleeding within the eye, retinal tear, retinal detachment, and infection of the eye. These complications are very rare, estimated to occur at a rate of 1 per 1,000 procedures, but may require surgery or other treatments, and may result in permanent loss of vision.

It is advised that you report all new symptoms to your study doctor as soon as possible if you are aware of symptoms, such as severe pain in the eye, more floaters or flashes, or worsening vision.

Risk of Brolucizumab

Brolucizumab is given by injection into the eye with a tiny needle. The drug has undergone many studies to assess its safety and effectiveness in treating AMD. Although rare, there are some risks associated with the use of this medication which are listed below.

Common Side Effects (1 to less than 10 in 100 participants receiving brolucizumab may have); decreased sharpness of vision (visual acuity reduced), clouding of the lens (cataract), bloodshot eye (conjunctival haemorrhage), small particles or spots drifting across the field of vision (vitreous floaters), eye pain, bleeding in the retina (retinal haemorrhage), detachment or tear of one of the layers at the back of the eye (vitreous detachment, retinal tear or retinal pigment epithelial tear), inflammation of tissues lining the inside of the eye (iritis, uveitis)\*, inflammation or scratching of the surface of the eye (conjunctivitis, punctate keratitis, corneal abrasion), allergic reactions (hypersensitivity), increase in the pressure within the eye (intraocular pressure increased)

Uncommon Side Effects (1 to less than 10 in 1000 participants receiving brolucizumab may have); redness of the eye (conjunctival hyperaemia), increased tear production (lacrimation increased), a feeling of having something in the eye (foreign body sensation in eyes), blindness, blockage of an artery in the eye (retinal artery occlusion), inflammation of the inside of the eye (vitritis, endophthalmitis), detachment of one of the layers in the back of the eye (retinal detachment, and detachment of retinal pigment epithelium) ,swelling in the front of the eye (corneal edema), eye inflammation (iridocyclitis, anterior chamber inflammation/flare), bleeding in the eye (vitreous haemorrhage)

\*In a large study for wet AMD (a disease associated with aging that gradually destroys sharp, central vision). Inflammation of tissues lining the inside of the eye (iritis, uveitis) was reported more often in Japanese participants compared to non-Japanese participants. However, these events in Japanese participants were either mild or moderate in severity (none were serious) and all resolved completely. Adverse events reported outside of the eye were similar between Japanese participants and non-Japanese participants.

Eye examinations

Use of drops to dilate the pupil is standard for any eye examination. Pupil dilation may cause temporary sensitivity to light and blurring of vision for several hours. It is recommended that you do not drive while your eyes are dilated.

1. **Potential Benefits**

You may not personally benefit from taking part in this study; however, the information gained from this study may help us learn more about the effectiveness and safety of brolucizumab which will help yourself and others with treatment of AMD in the future.

1. **Voluntary participation/right to refuse or withdraw**

There is no obligation for you to be involved in this study. If you choose not to participate your normal treatment plan will continue. There are other treatments available if you decide not to be part of the study. This may include staying with your current treatment or switching to a similar approved drug.

Brolucizumab is also available for your use should you choose not to participate in the trial. However, as it is not currently subsidised by the government, there would be a significant cost involved in order to obtain the medication.

Your study doctor will discuss appropriate treatment options and the risks and benefits with you whether you take part in the study or not.

If you decide to participate in the study and later feel that you no longer wish to be part of it, you may withdraw from the study at any time without prejudice to any current or future medical treatment. All information already collected as part of the study will be retained.

1. **Confidentiality**

All the information obtained in this study will be kept strictly confidential. All medical information will be de-identified and linked to a unique patient number. The only people with access to this information will be Dr Andrew Chang (Director, Sydney Retina Clinic & Day Surgery) and authorised researchers. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation.

1. **Payment/Costs**

The study drug, consultation fees and treatment costs for the study eye will be provided at no charge. You need to pay consultation and treatment costs in the fellow eye according to standard charge level at Sydney Retina Clinic and Day Surgery for each visit. No travel or parking fee will be reimbursed for taking part in this study. You should discuss with your study doctor regarding costs of visits and treatments.

1. **Illness or Injury**

If, as a result of being in this study, you become ill or are injured, please immediately contact your study doctor. She or he will then give you all necessary information and treatment and will inform the trial sponsor. In the case of a serious and rapidly escalating adverse reaction contact emergency services on 000.

1. **Compensation for injury**

You will not be paid or reimbursed for your participation in this study.

If, as a result of your participation in this study, you become ill or are injured, immediately advise your study doctor of your condition. In the first instance your study doctor will evaluate your condition and then discuss treatment with both you and your regular treating doctor. If you are unable to contact the study doctor, you should present immediately to the nearest hospital emergency department.

Since you are participating in a non-sponsored trial any question about compensation must initially be directed to your study doctor who will advise their insurer of the matter. It is the recommendation of the independent ethics committee responsible for the review of this trial that you seek independent legal advice.

1. **Termination of the study**

The study may be terminated from the study by Sydney Retina or Novartis Australia at any time. Reasons for terminating the study may include, but not limited to the following: unacceptable side effects, unsatisfied treatment results, unsatisfactory enrolment and inaccurate or incomplete data recording.

The reasons for termination of the study will be explained and you will receive the appropriate care for your condition. The Ethics Committee, the Therapeutic Goods Administration (TGA) may decide to stop the study and withdraw you from the study at any time, with or without your consent.

1. **Participant termination from the study**

The participant may be terminated from the study by Sydney retina or Novartis Australia at any time. Reasons for participant termination may include, but 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 and stage 3 or stage 4 macular holes.

The reasons for termination from the study will be explained to you and you will receive the appropriate care for your condition.

1. **New information arising during the study**

During the study, new information about the risks and benefits of the project may become known to the researchers. You will be told about this new information. This new information may mean that you can no longer participate in this study. If this occurs, the persons supervising the research project will stop your participation. You will be provided the appropriate care to suit your needs and medical condition.

1. **Results of Project**

Once the results are analysed, the results will be published in peer reviewed journals and presented at scientific journals.

1. **What happens when the research project ends?**

Study drug will not be provided after the end of the study, if you have discontinued or if you have been withdrawn from the study.

After the 12 month period of the study, you will revert back to the standard of care which you were receiving prior to the study or as discussed with your doctor.

Brolucizumab is available to you after the completion of the trial however as it is currently not subsidised by the government, there would be significant costs associated unless its subsidy status changes. This should be discussed with your treating physician to determine the best treatment suitable to you.

1. **Consent**

Your study doctor is required to provide you with all information regarding the nature and purpose of the research study, risks/benefits and the possibility of alternative treatment and you should be given the opportunity to discuss these. It must be stated that you are free to withdraw anytime and that if you do not participate you will not suffer any prejudice.

**Part 2 How is the research project being conducted?**

1. **What will happen to information about me?**

By signing the consent form, you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. Any information about you that is sent out of the hospital will have a pseudonymized code and will not show your name or address, or any information that directly identifies you. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant government health authorities, such as the Therapeutic Goods Administration (TGA), U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA) *,* the Human Research Ethics Committee that reviewed this project, the institution relevant to this Participant Information Sheet, Sydney Retina, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

All study information will be stored securely at Sydney Retina for the duration of the study and transferred to a secure storage facility. The information will be kept until at least 15 years following the closure of the study. After this time, it will be securely destroyed. Some of your study data will be sent overseas. The data protection laws governing data access and use in other countries may not be the same as those in Australia. If you have any questions about this, discuss them with your study doctor

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, unless you provide your permission.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and New South Wales privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

A description of this clinical trial will be available on www.ANZCTR.org.au, as required by the Australian National Statement on Ethical Conduct in Human Research. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website anytime.

1. **Further information**

**Further information and who to contact**

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on 9221 3755 or any of the following people:

**Clinical contact person**

|  |  |
| --- | --- |
| Name | Thomas Hong or Dr Ellie Bowditch (After hours) |
| Position | Research Manager/ Medical Registrar |
| Telephone | 9221 3755 / 0405 357 889 (Dr Bowditch- after hours) |
| Email | thong@sydneyretina.com.au / ebowditch@sydneyretina.com.au  |

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

**Complaints contact person**

|  |  |
| --- | --- |
| Name | Thomas Hong |
| Position | Research Manager |
| Telephone | 9221 3755 |
| Email | thong@sydneyretina.com.au |

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

|  |  |
| --- | --- |
| Reviewing HREC name | Bellberry Limited |
| HREC Executive Officer | Operations Manager |
| Telephone | +61 8 8361 3222 |
| Email | bellberry@bellberry.com.au |

**Reviewing HREC approving this research** **and HREC Executive Officer details**

The Bellberry Human Research Ethics Committee has reviewed this study in accordance with the National Statement on Ethical Conduct in Human Research (2007). Should you wish to discuss the study or view a copy of the Complaint procedure with someone not directly involved, particularly in relation to matters concerning policies, information or complaints about the conduct of the study or your rights as a participant, you may contact the Operations Manager, Bellberry Human Research Ethics Committee on 08 8361 3222.

All study participants should be provided with a copy of the Information Sheet and Consent Form for their personal records.

**Consent Form**

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

I the undersigned hereby voluntarily consent to my involvement in the research project titled “Brolucizumab Treatment for Pigment Epithelial Detachment in Treatment-Resistant Neovascular Age-Related Macular Degeneration”.

I acknowledge that the nature, purpose, risks and alternative treatments have been fully explained to my satisfaction by Dr Andrew Chang. I have also been provided with an Information Sheet regarding the research.

Specifically, the details of the procedure(s) proposed and the anticipated length of time it will take, the frequency with which the procedure(s) will be performed and an indication of any discomfort that may be expected have been explained to me.

* Although I understand that the purpose of this research study is to improve the quality of medical care, it has also been explained that my involvement may not be of any direct benefit to me.
* I have been given the opportunity to have a member of my family or another person present while the study is explained to me.
* I have been told that no information regarding my medical history will be divulged and the results of any tests involving me will not be published so as to reveal my identity.
* I understand that access will be required to my medical records for the purpose of this study as well as for quality assurance, auditing and in the event of a serious adverse event.
* I understand that if I become pregnant during the study I will be invited to consent to access to information regarding any pregnancy and its outcome.
* I understand that I am free to withdraw from the study at any stage without prejudice to future treatment. If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.
* I am 50 years of age or over.
* I consent to my GP being notified of my participation in this study and of any clinically relevant information noted by the trial doctor in the conduct of the trial.
* I declare that all my questions have been answered to my satisfaction.
* I have read, or have had read to me in my first language and I understand the Participant Information Sheet, version1.3 dated 4 March 2021.

SIGNATURE OF STUDY PARTICIPANT:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

DATE:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

NAME OF INVESTIGATOR: Andrew Chang

SIGNATURE OF INVESTIGATOR:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

DATE:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

In the event that a witness is present the following signing clause is to be used.

SIGNATURE OF WITNESS \_\_\_\_\_\_ DATED

FULL NAME OF WITNESS

ADDRESS

I declare that I have been present when the research was explained to the above participant and I believe that the participant has an appreciation and understanding of the explanation given and that the consent was freely given