Lions Eye Institute Clinical Trials Unit

INN: dexamethasone
INN: bevacizumab

Synopsis/Clinical Trial Protocol

A randomized clinical trial of intravitreal dexamethasOne versus bevacizumab in Aboriginal and Torres Strait Islander patientS with Diabetic Macular Oedema (The OASIS Study)

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Statement of Compliance

This study will be conducted in compliance with all the stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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List of abbreviations

AEs	adverse events
anti-VEGF	anti-vascular endothelial growth factor
ANZCRT	Australian New Zealand Clinical Trials Registry
BCVA	best corrected visual acuity
CA	California
CI	confidence interval
CMT	central macular thickness
CRT	central retinal thickness
CVA	cerebrovascular accident
DM	diabetes mellitus
DMO	diabetic macular oedema
DR	diabetic retinopathy
eCRF	electronic case report form
EOS	end of study
FDA	Food and Drug Administration
FFA	fundus fluorescein angiography
GCP	good clinical practice
IOP	intraocular pressure
IVT	intravitreal
LogMAR	logarithm of the minimum angle of resolution
OCT	ocular coherence tomography
PICF	participant information and consent form
q3m	every 3 months
q1m	every 1 month
SAEs	serious adverse events
SARs	serious adverse reactions
SD-OCT	spectral domain ocular coherence tomography
TIA	transient ischaemic attack

Protocol summary

Title:	A randomized clinical trial of intravitreal dexamethasone versus bevacizumab in Aboriginal and Torres Strait Islander patients with diabetic macular oedema (DMO) (The OASIS Study).
Short Title:	Intravitreal dexamethasone vs bevacizumab in Aboriginal people with DMO
Sponsor and	Lions Eye Institute, Western Australia.
Clinical phase	Phase IV clinical trial.
Purpose and rationale	The purpose of this study is to investigate the efficacy and safety of intravitreal (IVT) dexamethasone implant (Ozurdex) compared to bevacizumab (Avastin) for Aboriginal patients from Western Australia with diabetes mellitus and centre-involving DMO.
Primary Objective(s)	The difference in the change in best corrected visual acuity (BCVA) between participants receiving Ozurdex compared with those receiving Avastin.
Secondary Objectives	• To evaluate if the visual outcome of Ozurdex is similar to Avastin. • To evaluate if the anatomical outcome of Ozurdex is similar to Avastin. • To evaluate the safety profiles of Ozurdex and Avastin. • To compare Ozurdex and Avastin in terms of the number of attendances, and the number of injections. • To compare regional participants to metropolitan participants in terms of the primary and secondary objectives.
Study design	Prospective, phase IV multicentre, randomized, active-controlled, single-masked, non-inferiority clinical trial.
Population	Aboriginal and Torres Strait Islander patients with DMO, age 18 years and older.
Key Inclusion criteria	• Self-identifying as Aboriginal Australian or Torres Strait Islander. • Adult aged 18 years and over. • Diagnosis of diabetes mellitus (DM) type 1 or type 2. • BCVA of at best 0.2 logarithm of the minimum angle of resolution (LogMAR) (20/32) 6/9 in the study eye. • Pseudophakic, OR phakic eyes with significant lens opacity, and scheduled to undergo cataract surgery at the time of enrolment. • Presence of any grade of diabetic retinopathy (DR) with centre-involving/threatening DMO, as defined by clinical examination and ocular coherence tomography (OCT) scan findings.
Key Exclusion criteria	• Intervention: Previous treatment in the study eye, including at the time of the first trial treatment with: - IVT anti-vascular endothelial growth factor (anti-VEGF) injections within the last 6 weeks; - Macular laser within the last 4 months; - IVT triamcinolone or triescence within the last 6 months; or at the time of the first trial treatment. • History of open-angle glaucoma or steroid-induced intraocular pressure (IOP) elevation that required IOP-lowering treatment, or IOP ≥25 (Goldmann applanation) on 2 consecutive clinic visits. • Eyes with concurrent ocular pathology other than DMO or cataract-causing visual loss, including macular ischaemia as determined by clinical examination and fundus fluorescein angiography (FFA) imaging.

- Women who are breastfeeding, confirmed as pregnant or planning on becoming pregnant in the next 6-12 months.
- Participants for whom Ozurdex or Avastin treatment are contraindicated as per product information:
  - Active or suspected ocular/periocular infections, including most viral diseases of the cornea and conjunctiva, active epithelia herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
  - Aphakic eyes with rupture of the posterior lens capsule.
  - Eyes with an anterior chamber intraocular lens and rupture of the posterior lens capsule.
  - Known angina, myocardial infarction, transient ischaemic attack (TIA) or cerebrovascular accident (CVA) in the last 3 months.
  - Known hypersensitivity to any components of these products

Study treatment

Dexamethasone IVT implant (Ozurdex) 0.7 mg
Bevacizumab IVT injection (Avastin) 1.25 mg/0.05 mL

Primary outcome

The primary outcome measure will be the difference in the BCVA change from baseline to 12 months between the two treatment arms, with a non-inferiority margin of 0.1 LogMAR (equivalent to one line of Snellen visual acuity). The BCVA will be measured for all study participants, at each clinic visit.

Secondary outcomes

1. BCVA loss or gain: The proportion of participants with a BCVA loss or gain of <0.3 LogMAR ('stable BCVA'), a BCVA loss of ≥0.3 LogMAR ('decline in BCVA'), or a BCVA gain of ≥0.3 LogMAR ('gain in BCVA');
2. Change in the central macular thickness (CMT) from baseline to 12 months as measured by OCT;
3. Number of IVT injections administered per participant;
4. Number of appointments attended per participant;
5. Intraocular pressure: The change in the mean IOP, the number of participants with one or more occasions of IOP elevation >28 mmHg, an increase in IOP by >10 mmHg from baseline to 12 months, and an IOP elevation requiring medical, laser or surgical treatment.

Safety outcomes

Safety assessments will include ophthalmic examinations and IOP measurements as well as recording the type, frequency and severity for all adverse events (AEs).

Statistical methods

Snellen visual acuity measurements will be converted to LogMAR for statistical analysis and reporting. Non-inferiority will be confirmed, if the non-inferiority margin of 0.1 LogMAR is not exceeded. For secondary outcomes, which include a change in the CMT, descriptive statistics of the mean number of injections and attendances, and mean IOP will be analysed. The safety endpoints include descriptive statistics of AEs and SAEs (serious adverse events).

Subgroups

The subgroup analysis will be performed on participant data from regional areas versus from metropolitan areas. The primary and secondary outcomes will be compared between the groups.

Key words

Diabetes mellitus, diabetic macular oedema, Ozurdex, Avastin, dexamethasone implant, bevacizumab

1 Introduction

1.1 Lay title and description

DMO is the most common cause of visual loss in people with diabetes. Regular injections of bevacizumab (Avastin) given as frequently as every month remain the current standard of care for centre-involving DMO; however, this regimen is impractical for many Aboriginal patients. Using Ozurdex implants every 3-6 months could be as effective as the currently used Avastin injections. In order to address this real-world problem, this study seeks to investigate whether it is possible to safely use a long-acting steroid preparation such as the dexamethasone IVT implant (Ozurdex) to manage DMO in Aboriginal patients living in Western Australia.

1.2 Background

The prevalence of self-reported DM in Aboriginal Australians is reported to be as high as 38%[1]. Despite gradual improvements in underlying social determinants of health, the high morbidity and mortality attributed to DM in Aboriginal populations indicates significant ongoing issues with adherence to screening and treatment regimens[2]. The greater prevalence of DM in the Aboriginal Australian population would be expected to account (at least in part) for the observed complication rates, including DR.

The pooled prevalence data for DR in known diabetics, reported in the Aboriginal Australian studies published within the last 30 years indicate a prevalence of any DR of 23%[3]. Furthermore, a significantly higher rate of DMO has been shown in Aboriginal Australians compared with non-Aboriginal Australians (7.6% versus 4.9% respectively)[3]. Assuming a total Aboriginal Australian population of 669,900[4], these figures suggest that there are currently up to 19,000 Aboriginal Australians with DMO, making up approximately 3% of the Aboriginal Australian population. An earlier-age onset of type 2 DM resulting in a more aggressive phenotype of DR[5], combined with a faster progression of retinopathy due to delays in DM diagnosis, poor glycaemic control[6,7], and inadequate risk factor management[8,9] underlies the increased numbers of Aboriginal Australians that ultimately progress to vision-threatening DR, including DMO.

DMO is characterised by swelling of the central retina. The hypoxic retinal conditions in diabetic individuals result in structural changes in the vessel walls and a functional impairment of the blood-retinal barrier. The resultant increase in vascular permeability causes retinal oedema, and loss of central vision ensues when oedema involves the macula. Treatment is aimed at reducing visual loss by targeting factors involved in the activated hypoxia pathway, or with laser targeting dysfunctional blood vessels to limit leakage. Laser was the first treatment shown to effectively reduce DMO and improve vision; however, it cannot be applied to the very centre of the macula[10]. More recently, DMO has been shown to respond to intraocular injections with anti-VEGF agents (bevacizumab, ranibizumab, and aflibercept), reducing reliance on laser treatments. In fact, for patients in whom the very centre of the macula is involved, and who have moderately reduced vision, monthly IVT injections with anti-VEGF agents were shown to be superior to laser treatment in improving vision provided a high level of compliance is achieved[11,12].

Corticosteroids are anti-inflammatory agents with anti-VEGF and anti-proliferative effects. Unfortunately, the increased rates of cataract and elevated IOP are the main adverse effects of the IVT corticosteroid treatments, including triamcinolone, making this a less-appealing option than anti-VEGF agents[13]. However, their efficacy has been demonstrated in a subgroup of pseudophakic patients with DMO, where triamcinolone plus laser treatment was shown to be superior to laser treatment alone, and equivalent to ranibizumab (alone or with laser treatment)[13]. First-line treatment with triamcinolone is also the most cost-effective option for pseudophakic patients[14]. Thus, IVT triamcinolone is considered one of the effective adjunct modalities for the treatment of DMO and has emerged as an alternative therapy to anti-VEGF agents for persistent or refractory DMO[15].

The progression of DMO after cataract surgery is frequently observed, particularly in patients with pre-existing DR and DMO [16]. Recent studies have shown short-term benefits of adjuvant therapy with IVT bevacizumab and/or triamcinolone administered during cataract surgery for patients with pre-existing DMO as well as in diabetic patients with DR without retinal thickening [17]. However, frequent post-operative review and re-injection of these short-acting agents remains a major limitation.

Ozurdex (Allergan, Irvine, CA, United States) is a unique biodegradable dexamethasone IVT implant. This slow-release preparation of dexamethasone (a highly potent steroid with a short half-life) has greater long-term efficacy than conventional forms of IVT triamcinolone, with the IVT concentration peaking within 3 months and sustained for up to 6 months post injection[18]. This translates clinically to less frequent injections than conventional treatment with monthly IVT triamcinolone [19-21]. Although the Food and Drug Administration (FDA) initially approved it only for macular oedema secondary to retinal vein occlusion, and non-infectious posterior uveitis; increasing short-term evidence of its efficacy in the treatment of DMO has resulted in the recent approval of Ozurdex for this indication [22,23]. The geography and population being studied in this trial create some unique challenges, which demand a more flexible study protocol. Longer-acting IVT agents such as Ozurdex have the potential to significantly improve DMO-associated visual morbidity with greater feasibility when used for Aboriginal patients with or at risk of DMO.

1.3 Purpose

The purpose of this study is to demonstrate the similar efficacy and safety of the IVT dexamethasone implant (Ozurdex) and IVT bevacizumab (Avastin) for Aboriginal patients from Western Australia with DM and active (centre-involving/threatening) DMO. For patients who are scheduled for cataract surgery, and randomized to receive Ozurdex, the use of Ozurdex is considered 'on-label'. This reflects the current real-world practice in Australia, where these patients are currently treated with an 'off-label' injection of Avastin or triamcinolone at the time of cataract surgery to mitigate the risk of post-operative DMO. The use of Ozurdex for this trial has been approved by the manufacturer (Allergan, Irvine, CA, United States).

2 Objectives and endpoints

Table 1. Objectives and related endpoints

Objective(s)	**Endpoint(s)**
Primary Objective(s) • To demonstrate the non-inferiority of Ozurdex to Avastin, in terms of BCVA	Endpoint(s) for primary objective(s) • The upper bound of the 90% confidence interval (CI) of the difference between the mean change in the BCVA from baseline to 12 months between the two treatment arms.
Secondary Objective(s) • To evaluate whether the visual outcome of Ozurdex is similar to Avastin • To evaluate whether the anatomical outcome of Ozurdex is similar to Avastin • To evaluate whether Ozurdex is similar to Avastin in terms of safety • To evaluate how Ozurdex compares to Avastin, in terms of the number of clinic attendances and the number of injections	Endpoint(s) for secondary objective(s) • Mean change in the BCVA from baseline to month 12 • Mean change in the CMT using spectral domain ocular coherence tomography (SD-OCT) from baseline to month 12 • Incidence of ocular and non-ocular AEs over 12 months Mean number of attendances and mean number of injections for each study arm

- To compare how regional participants compare to metropolitan participants in terms of the primary and secondary objectives.
- Subgroup analysis of regional versus metropolitan participants comparing non-inferiority outcomes, visual outcomes, anatomical outcomes, and safety outcomes.

2.1 Primary outcome measure

The primary outcome measure will be the difference in the BCVA change from baseline to 12 months between treatment arms, with a non-inferiority margin of 0.1 LogMAR (equivalent to one line of Snellen visual acuity). The BCVA will be measured for all study participants at each clinic visit.

2.2 Secondary outcome measures

Secondary outcome measures will include:

1. BCVA loss or gain: The proportion of participants with a BCVA loss or gain of <0.3 LogMAR (termed 'stable BCVA'), a BCVA loss of ≥0.3 LogMAR ('decline in BCVA'), or a BCVA gain of ≥0.3 LogMAR ('gain in BCVA');
2. Change in the CMT from baseline to 12 months as measured by OCT;
3. Number of IVT injections given per participant;
4. Number of appointments attended per participant;
5. IOP: The change in the mean IOP, the number of participants with one or more occasions of IOP elevation >28 mmHg, an increase in the IOP by >10 mmHg from baseline to 12 months, and an IOP elevation requiring medical, laser or surgical treatment.

3 Study design

This is a multicentre, randomized, active-controlled, single-masked, non-inferiority clinical trial in Aboriginal patients with DMO; with a total duration of 54 weeks. A total of 50 eyes will be randomized at baseline in a 1:1 ratio into two treatment groups. The randomization will be stratified by age, and rurality status.

All participants will have a baseline assessment, including comprehensive clinical examination, colour fundus photography, and an OCT scan. FFA and other retinal imaging (e.g. ultra-wide field) will be performed where indicated and practicable.

The study consists of two periods: a screening period of up to 2 weeks (+1 in case of technical errors, e.g. images of insufficient quality) to assess the participant's eligibility, and the treatment period (baseline to month 12). An outline of the study period is presented in Figure 1, and a detailed visit and assessment schedule is provided in Table 4.

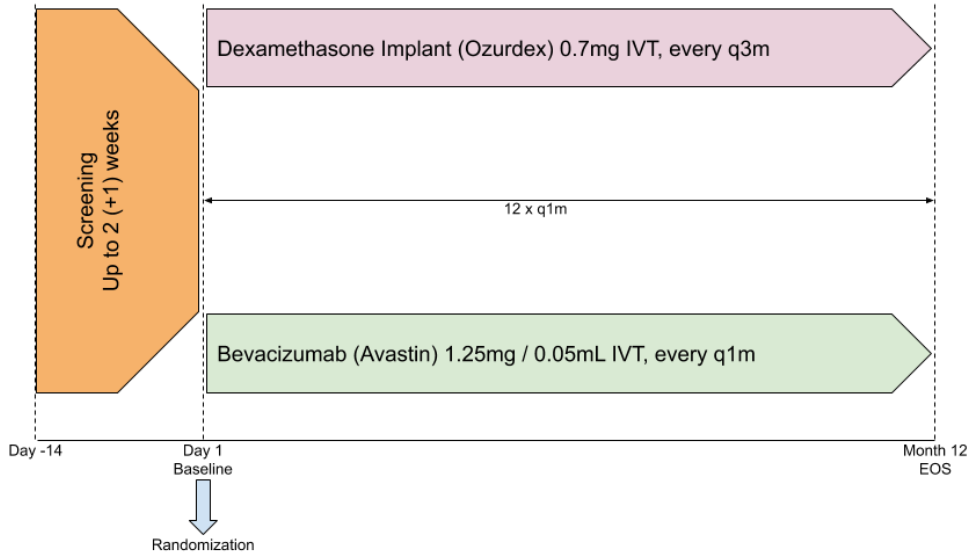

Figure 1. Study design.

Screening Period (screening to randomization, day 14 to baseline)

The screening period begins with the first screening procedure, once the participant has provided written informed consent to participate in the study, and ends at the randomization visit (baseline) of the study. The screening period of up to 2 (+1) weeks will be used to assess the eligibility of the participants. As participants with DMO require therapeutic intervention, the screening period must be kept as short as possible. The participants must have the diagnosis of DMO in the study eye confirmed at screening.

Treatment Period (baseline to month 12)

Both eyes may be included in the study, if they meet the inclusion criteria. The treatment period begins with randomization (baseline) and ends with the completion of month 12 assessments. After confirmation of eligibility, the participants will be randomized in a 1:1 ratio into either the dexamethasone implant group or the bevacizumab injection treatment group. During the treatment period, the participants in the dexamethasone treatment arm will receive a single IVT injection of 0.7 mg dexamethasone implant every 3 months, and participants in the bevacizumab treatment arm will receive a single IVT injection of 1.25 mg/0.05 mL bevacizumab each month.

A study visit schedule will be established at the time of randomization for all the participants. Every effort should be made by all the participants to adhere to all the scheduled visits and assessments as outlined in the assessment schedule or as close to the designated day/time as possible (Table 4. Assessment schedule). All efforts should be made to revert back to the planned visit schedule, taking into consideration the restriction on the minimum treatment interval for the study treatment. Month 11 corresponds to the last treatment.

4 Rationale

4.1 Rationale for study design

Due to the high rates of type 2 DM, Aboriginal Australians account for 16% of all Australians with vision-threatening DR, despite making up only 2.5% of the Australian population. The prevalence of DMO, a subset of vision-threatening DR, is both significantly greater in Aboriginal Australians than for non-Aboriginal Australians, and out of proportion to the rate of DM. DMO is responsible for greater visual morbidity than other vision-threatening ocular diseases[25], and incurs significantly higher health-care costs than those without retinopathy[26]; therefore, tackling this disease should be high priority.

Although IVT anti-VEGF agents are currently the initial standard of care for DMO, they bear the disadvantage of requiring monthly injections or evaluations at least for the first 12 months of treatment. The direct application of this type of protocol is impractical in some populations where compliance with treatment is a significant issue, or the access to ophthalmology services is limited. In rural and remote Western Australia, difficult communication, extreme travel distances, and competing priorities result in non-attendance, making visual outcomes inferior to those seen in strictly run clinical trials. It is therefore imperative that the systems are tailored to the specific needs of this population. With the advent of a slow-release steroid preparation such as the dexamethasone IVT implant Ozurdex, it would be valuable to determine if it is possible to gain at least equal control of DMO with less frequent reviews and treatments than with the use of the currently used anti-VEGF, Avastin. If a practical regimen is found to work at least as well as the existing combination of laser and Avastin injections, then it may have implications for managing DMO in remote Australia as well as many third-world settings globally, where regular and frequent attendance is often not possible.

A better understanding of the unique aspects of diabetic retinopathy and the response to treatment in Aboriginal Australians warrants further study. An identification of epidemiological patterns is required to recognise the relative risks for DR in Aboriginal populations. Understanding the underlying susceptibility to DR and the differential responses to treatment will support the development of targeted screening and treatment strategies, and ultimately determine appropriate strategies to reduce vision loss from DM in Aboriginal Australians.

This study was designed to assess the safety and efficacy of the dexamethasone implant versus bevacuzimab for the treatment of DMO in Aboriginal patients. Dexamethasone is safe and effective as a second-line treatment of DMO in conditions where the patient has refractory DMO, is pseudophakic, and there is regular IOP monitoring. Given the longer duration of action, the real-world practice for Aboriginal patients with barriers to accessing a regular follow-up has been to use a dexamethasone implant for DMO. A randomized control trial design aims to address the question of safety and efficacy for this practice.

The assessment schedule is the same for both treatment arms, despite the differences in the drug administration schedules. This is to collect efficacy data for the entire duration of action of the dexamethasone implant; safety measures and AEs are measured at each visit to evaluate the assessment compliance between the groups.

The overall non-inferiority trial design resembles that of similar studies investigating the non-inferiority of other anti-VEGF drugs against each other. The proposed treatment scheme and dosing is in line with the authorized label and standard of care.

Equivalence testing related to the primary efficacy parameter BCVA will be based on a non-inferiority margin of 0.1 LogMAR. A change in the BCVA of >0.1 LogMAR (1 Snellen line equivalent) is considered relevant in clinical practice, regardless of the underlying disease. Therefore, this equivalence margin provides assurance that any proof of equivalence only occurs, if the observed treatment differences are of no clinical relevance.

4.2 Rationale for dose/regimen and duration of treatment

The dosing of dexamethasone is chosen according to the known duration of action of the implant, the dexamethasone implant pivotal clinical trials in DMO, and the data from real-world practice.

4.3 Rationale for the choice of comparator

Bevacizumab was chosen as it is the most common IVT injection used in regional Western Australia for DMO, according to recent audit data. The choice reflects the pharmaceutical funding structures in Australia, which make it the cheapest and most widely accessible drug for the indication; an important consideration

for the target population. The dosing for bevacizumab was chosen according to the pivotal clinical trials in DMO.

4.4 Risks and benefits

The risks to the participants in this study can be minimized by compliance with the eligibility criteria and the study procedures as well as close clinical monitoring for any safety signals.

Avastin has been licensed and commercialized globally since 1997, while Ozurdex has been licensed and commercialized globally since 2009. Clinical studies provided evidence of efficacy and safety for both drugs in all approved indications, including DMO. Since approval, an extensive post-marketing experience has been gathered, which confirms the established safety and efficacy profiles, and demonstrates the favourable risk-benefit ratios for Avastin and Ozurdex.

In terms of the safety profile, Avastin is well-tolerated across all indications. Commonly reported AEs include conjunctival haemorrhage, eye pain, and transient rises in IOP. The SAEs are rare and include retinal detachment, bacterial endophthalmitis, and sterile endophthalmitis. Bevacizumab has 3 black box warnings: gastrointestinal perforation, surgery and wound healing complications, and severe or fatal haemorrhage. However, the risk of these SAEs are thought to be very low as the IVT dose is 300-500 times lower than the intravenous dose.

The most common AEs for Ozurdex are conjunctival haemorrhage, eye pain, floaters, rises in IOP, and posterior sub-capsular cataract. The SAEs include those of Avastin, and the risk of a significant rise in IOP is greater for Ozurdex.

5 Study population

The study will enrol male and female patients who are aged 18 years or older with a diagnosis of DM, patients with DR, and centre-involving DMO.

5.1 Inclusion criteria

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

- Self-identifying as Aboriginal Australian or Torres Strait Islander
- Adults aged 18 years and over
- Diagnosis of DM (type 1 or type 2)
- BCVA of at best 0.2 LogMAR (20/32) 6/9 in the study eye
- Pseudophakic, or phakic with significant lens opacity and scheduled to undergo cataract surgery at the time of enrolment
- Presence of any grade of DR with centre-involving DMO, as defined by clinical examination and OCT scan findings
    - Active DMO: Centre-involving/threatening DMO, as defined by clinical examination and OCT scan findings.
    - At risk of DMO: Patients scheduled for cataract surgery with non-centre involving DMO who are assessed as being at risk of post-operative centre-involving DMO based on clinical examination, OCT scan findings, and Investigator discretion.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for this study:

- Intervention: Previous treatment in the study eye including at the time of the first trial treatment with:
    - IVT anti-VEGF injections within the last six weeks;
    - Macular laser treatment within the last four months;
    - IVT triamcinolone or triescence within the last six months; at the time of the first trial treatment.
- History of open-angle glaucoma or steroid-induced IOP elevation that required IOP-lowering treatment or, IOP ≥25 (Goldmann applanation) on two consecutive clinic visits.
- Eyes with concurrent ocular pathology other than DMO, or a cataract-causing visual loss, including macular ischaemia as determined by clinical examination and FFA imaging.
- Women who are breastfeeding, confirmed as pregnant or planning on becoming pregnant in the next 6-12 months.
- Participants for whom Ozurdex or Avastin treatment are contraindicated as per product information:
    - Active or suspected ocular/periocular infections, including most viral diseases of the cornea and conjunctiva, active epithelia herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases.
    - Aphakic eyes with rupture of the posterior lens capsule.
    - Eyes with an anterior chamber intraocular lens and rupture of the posterior lens capsule.
    - Known angina, myocardial infarction, TIA or CVA in the last three months.
    - Known hypersensitivity to any components of these products.

6 Treatment

6.1 Study treatment

The study medications, Ozurdex and Avastin will be supplied in their original manufacturer's packaging, Ozurdex as a 0.7 mg IVT implant in a pre-loaded 22-gauge needle with an applicator, and Avastin 1.25 mg/0.05 mL in a 1 mL pre-filled syringe with a 30-gauge needle. The Sponsors will ensure sufficient supplies of Ozurdex and Avastin for treatment to allow for the completion of the study.

6.1.1 Investigational and control drugs

Table 2. Investigational and comparison drugs

Investigation/comparison drug (Name and Strength)	Pharmaceutical dosage form	Route of Administration	Supply Type	Sponsor (global or local)
Ozurdex (0.7 mg)	Dissolvable implant	Intravitreal	Pre-loaded applicator	Sponsor (global)
Avastin (1.25 mg/0.05 mL)	Solution for injection	Intravitreal	Pre-filled syringe	Sponsor (local)

6.1.2 Additional study treatments

No other treatment beyond the investigational drug and the comparator drug are included in this trial.

6.1.3 Treatment arms/groups

Participants will be assigned at the baseline visit to one of the following two treatment arms/groups with approximately 25 participants in each arm in a ratio of 1:1.

- Ozurdex: IVT administration of 0.7 mg Ozurdex in the study eye, every three months (q3m) at baseline, month 3, month 6, and month 9; with monthly intervening clinic review visits.
- Avastin: IVT administration of 1.25 mg/0.05 mL Avastin in the study eye, every one month (q1m) at baseline, months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11.

6.1.4 Treatment duration

The planned duration of treatment is 12 months as discussed in 3. Study design. The discontinuation of the study treatment for a participant occurs when the study drug is stopped earlier than the protocol planned duration, and can be initiated by either the participant or the Investigator. The participants who prematurely discontinue the study treatment for any reason except withdrawal of consent should have the end of study (EOS) visit scheduled one month after the last study-treatment administration. For discontinuation details, see 9. Study discontinuation and completion below.

6.2 Other treatment(s)

In the study eye, cataract surgery, focal macular laser treatment, pan retinal photocoagulation laser treatment, and glaucoma therapy (topical antihypertensive drops, selective laser trabeculoplasty laser or drainage surgery) can be performed as necessary by the study Investigators. Such treatment in the study eye is to be recorded and reported in the electronic case report form (eCRF) throughout the course of the study.

6.2.1 Concomitant therapy

The Investigators must record in the eCRF, the administration of any medications, procedures, and significant non-drug therapies. In addition, information about any medications and procedures performed in the 90 days preceding enrolment should also be recorded.

If the participants' fellow eyes develop DMO or any other conditions in the duration of the study, the Investigator can treat them with the standard of care and record this in the eCRF. This treatment should be conducted and followed up according to routine practice guidelines and any AEs should be recorded in the eCRF.

Each concomitant drug that is considered for treatment of the participants must not be in the list of exclusions and/or prohibited medications. If the Investigator is unsure about including a participant or retaining a participant because of a particular medication, he/she should consult the Sponsor to decide whether the participant can be retained or enrolled in the study.

6.2.2 Prohibited medication

Table 3. Prohibited medication has a list of medications that participants should not use for the duration of this study. If any participants use any of these medications/treatments, they will cease to be study participants and will be excluded from the study treatments. Medications and treatments necessary for treating ocular or systemic AEs are permissible and need to be noted in the eCRF.

Routine standard-of-care treatments for fellow-eye conditions are allowed and must be recorded in the eCRF.

Table 3. Prohibited medication

Medication	**Action taken**
Study eye: Intra- or periocular corticosteroids other than the study treatment	Discontinue study treatment
Study eye: Anti-VEGF therapy other than the study treatment	Discontinue study treatment
Systemic: Systemic corticosteroids for 15 or more consecutive days	Discontinue study treatment
Systemic: Systemic anti-VEGF therapy	
Study eye, fellow eye, and systemic: Any investigational drug,	

biological, or device (with the exception of over-the-counter vitamins, supplements or diets).	Discontinue study treatment Discontinue study treatment

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a participant number, which is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the study. A new participant number consists of a sequential participant number with a study eye 'R' or 'L' suffix to it, so that each study eye is numbered uniquely across the entire database. Upon signing the consent form, the participant is assigned to the next available sequential participant number.

6.3.2 Treatment assignment and randomization

The participants who meet the eligibility criteria and consent to trial enrolment will be randomized using an online true random number generator (https://www.random.org). The randomization will occur in blocks of four participants at a time until a total of 50 participants is reached.

Phakic patients (with or at risk of DMO) will be randomized to receive cataract surgery if indicated, with either peri-operative IVT Avastin or peri-operative IVT Ozurdex at baseline or mid-trial depending on the clinical grading of the cataract. The phakic patients randomized to Ozurdex will require waitlisting for cataract surgery as per PBS requirements. The pseudophakic patients (with active DMO) will be randomized to receive either IVT Avastin or IVT Ozurdex. This study aims to exclusively enrol diabetic Aboriginal Australians living in Western Australia.

Both eyes may be enrolled, if they meet the eligibility criteria for the study. In these patients, the sequence of enrolment and treatment will be based on the treating Investigator's clinical recommendation and informed discussions with the trial participants. The patients with only one functioning eye need not be specifically excluded if the remaining criteria are satisfied.

6.4 Treatment masking

This is a single-masked trial with participant masking. The allocated treatments will be concealed in sealed opaque envelopes. The treating ophthalmologist will not be blinded to the treatment allocation.

The treating Investigators, the trial coordinator, and the Aboriginal Eye Health Coordinator will be unmasked to the treatment allocation. The Investigators who examine the patients on review visits may also be unmasked since the Ozurdex implant is visible in the vitreous cavity. The other non-treating Investigators, trial staff, and study participants will be masked. It is anticipated that some study participants receiving Ozurdex may experience visual symptoms (due to the dimensions of the rod-shaped implant) that will differ from those receiving Avastin. This could potentially result in the participants interpreting the agent they have received, and being unmasked. This is considered to be a small, unavoidable and acceptable risk for this study.

6.5 Dose escalation and dose modification

Adjusting the study treatment dose is prohibited. In case of AEs, the study treatments can be suspended at the discretion of the Investigator.

6.6 Recommended treatment of adverse events

In case of any AEs, the Investigators will follow local guidelines, and practice their optimum medical judgement. All the treatments administered for the AEs should be noted in the eCRF.

6.7 Preparation and dispensation

6.7.1 Handling of the study treatment and additional treatment

A designated person must be present at the study site to receive the study treatments from the Sponsor. These should be handled and stored according to label instructions in a secure location. The labels should be in the local language, fulfil legal requirements and specify the conditions for storing the treatments for the study duration. They should be accessed and dispensed only by the assigned team members as per study protocol. At the end of the study, all remaining unused treatments must be sent back by the site pharmacist or designated person in consultation with the investigative team.

6.7.2 Instructions for prescribing and taking the study treatment

The participants should receive the appropriate assigned treatment in the study eye on the same day as the study visit or in the next three days. The only exception is the baseline visit, where treatment should be completed within the following 24 hours. When the assessments and treatments occur on the same day, the treatments should be administered after the efficacy assessments described in 8.3 Efficacy and pre-injection safety measures (tonometry, slit lamp and fundus examinations) and 8.4.1 Complete ophthalmic examination are completed. In case the study visit assessments and study treatment are conducted on separate days, a safety-check should be performed again before any treatment is administered and these assessment observations noted in the source documents. Administration of the study treatment will be cancelled, in case the Investigator flags any safety concerns about the study eye, that in the Investigator's opinion are the result of the study treatment or injection procedure; and AEs will be documented in the eCRF.

Each participant according to their randomization will be administered either an IVT injection of 1.25 mg/0.05 ml Avastin or 0.7 mg Ozurdex. The participants in the Ozurdex implant group who are phakic and require cataract surgery, will receive the Ozurdex intra- or peri-operatively. The participants from this group who are pseudophakic or phakic and still waitlisted on the cataract surgery list will be administered the treatment as outpatients. Both IVT injection treatments (Avastin and Ozurdex) will follow the injection technique protocol by the Flinders Medical Centre (South Australia) which has been proven to be acceptable and pain free for the participants (RANZCO, Hobart 2013).

Before administering the treatment, the Investigators should ensure that the participants do not have active ocular or periocular infections, and active intraocular inflammation in the study eye as the IVT injections are contraindicated in these circumstances.

Adjusting the study treatment dose is prohibited and study treatments can be suspended at the discretion of the Investigator in case of AEs.

7 Informed consent procedures

The patients eligible for this study can only be included as participants after completing informed consent procedures, including witnesses where required by law or regulation.

If the eligible participant has a representative(s) or legal representative(s) who provides the informed consent, it should be given after the participant has been told about the study commensurate to his/her comprehension. Where possible, the participant himself/herself should indicate their informed consent by signing and dating the documentation.

The participant must be able to read, comprehend, and agree to signing the informed consent documents. If the participant is hindered by visual impairment, they should be read the informed consent verbatim by an impartial witness or family member.

Participants must provide signed informed consent prior to the initiation of any study assessments, protocols, processes, and procedures. Each participant or their representative (legal) will be given a completed signed and dated participant information and consent form (PICF) copy. The original completed PICF will be retained in the Investigator's site file or, if locally required, in the participant's medical notes at the clinic or institution.

8 Visit schedule and assessments

An assessment schedule for every study assessment and treatment to be conducted from baseline is shown in Table 4. This schedule will be calculated for each participant from the day of their baseline visit. The participants and Investigators should make a concerted effort to follow the schedule for all treatments and assessments as closely as possible. At each visit, the assessments should be conducted before any treatment is administered and these assessment observations noted.

Participants should not be automatically excluded from the study because of missing or rescheduling of visits. The participants who wish to opt out of the study for personal or other reasons should be booked for a visit at the earliest, when all the EOS assessments can be completed.

Table 4. Assessment schedule

Period		**Treatment**												
Visit type	**Screening**	**Baseline**	**Treatment period**											
Month			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit number	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
Obtain informed consent	X													
Randomization		X												
Demography	X													
Inclusion/exclusion criteria	X	X												
Medical history	X													
Prior/concomitant medications	X													
Complete ophthalmic exam[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BCVA[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ozurdex administration		X			X			X			X			
Avastin administration		X	X	X	X	X	X	X	X	X	X	X	X	
Post-injection assessment[3]		X	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1]Includes slit-lamp examination, IOP measurement, and fundus examination. Dilation for the fundus examination is at the discretion of the Investigator. The ophthalmic examination will be performed for both eyes at the screening. All other evaluations are in the study eye only or also in the fellow eye at the discretion of the Investigator.

[2]BCVA must be performed at the screening and baseline visits to qualify the participant; the assessments will be performed prior to the IVT injections; BCVA and SD-OCT will be performed in the study eye at all the visits and in the fellow eye at screening only.

[3]The study eye will be evaluated 0-5 minutes and 30-60 minutes post injection, to ensure that the injection procedure and/or the investigational product have not endangered the health of the eye. It includes an evaluation of the central retinal artery perfusion via gross assessment of vision and the measurement of IOP. Direct visualization to assess the central retinal artery, the presence of retinal detachment, and the presence of new intraocular haemorrhage(s) could be at the discretion of the Investigator and/or based on the results of the gross assessment of vision and IOP measurement. The participants should be instructed to contact the Investigator immediately to report symptoms including eye pain, redness of the eye, photophobia, blurring of vision.

AEs, adverse events; BCVA, best corrected visual acuity; IOP, intraocular pressure; SD-OCT, spectral domain ocular coherence tomography.

8.1 Screening

Prior to any study procedures including screening; participants must complete, sign and date the PICF. Screening participants for the study is the beginning of the screening process, which takes place after accepting the PICF. This screening process can progress over several days, although it must be completed in 2 (+1) weeks before randomly assigning the participants to one of the two groups. Screening procedures include:

- Completing signed informed consent
- Demographic and medical history, including medications used 90 days before the study and/or on-going medications for the duration of the study
- BCVA in the study eye and fellow eye
- Complete ophthalmic examination of both eyes, including a slit-lamp examination, IOP measurement, and a fundus examination
- Digital colour fundus photography and SD-OCT of both eyes
- Participant registration
- Monitoring/reporting AEs
- Organizing a baseline visit

8.2 Participant demographics/other baseline characteristics

Participant information gathered at baseline will include demographic and baseline characteristics including age at screening, sex, relevant medical history/current medical conditions present prior to signing the PICF, past and present medications, initial diagnosis of DM, elapse in years after the diagnosis of DM (in years), primary diagnosis of DMO, unilateral or bilateral DMO, definition of the study eye, IOP, BCVA (Snellen chart), ophthalmic examinations, retinal imaging, OCT, CMT, and AEs.

8.3 Efficacy

Assessment of parameters to compare the efficacy of Ozurdex and Avastin:

- BCVA scores (with Snellen charts at 6 metres and conversion to the LogMAR equivalent
- CMT using SD-OCT

All the efficacy assessments should be conducted before any study treatments are administered.

8.3.1 Visual acuity

Prior to conducting any examination that needs contact with the eye or the application of eye drops for dilating the eye, the visual acuity assessments should be complete. These assessments will be performed at every study visit for the study eye, while the fellow eye will be examined only at the screening visit. BCVA will be measured using Snellen visual acuity testing charts with the participant in a sitting position.

8.3.2 Spectral-domain optical coherence tomography (SD-OCT)

SD-OCT will be performed at screening only for the fellow eye; however, the study eye will be assessed at every scheduled visit. A trained technician or the Investigator will conduct the SD-OCT assessments after the BCVA assessment and before any study treatments are administered to the study participants. The same SD-OCT machine will be used for the same participants throughout the study. SD-OCT will be used to measure the CMT, which is the average retinal thickness of the circular area within a 1-mm diameter around the foveal centre.

8.3.3 Appropriateness of efficacy assessments

The efficacy assessment procedures selected for this study are routine standard treatments for the medical condition and well-known in ophthalmologic clinical practice and clinical research. The imaging

assessments and SD-OCT are routinely-used diagnostic tools from the registration studies of Avastin, and other anti-VEGF therapies. Well-established standard study procedures related to the assessment of efficacy are utilised in this study.

8.4 Safety

The safety assessments to be conducted consist of ophthalmic examinations, IOP measurements, and records of the type, frequency, and severity for each of the AEs. These details will be collated under 10.1.1 Adverse events.

8.4.1 Complete ophthalmic examination

This will include:

- A slit-lamp examination, including an evaluation of the lids/lashes, conjunctiva, cornea, iris, lens, and aqueous reaction (cells and flare). This examination will be performed at every scheduled visit for the study eye and any significant abnormalities will be noted in eCRF on the AEs page by the masked Investigator.
- IOP measurements: These will be performed using an applanation tonometer, Tonopen ® (Reicherth inc., Buffalo, USA) or iCare device (Icare Finland Oy, Vantaa, Finland), whichever is available at the study site. The IOP measurements will be performed by the same method for the participant for the duration of the study. The Investigator will measure the IOP in the study eye in mmHg before and after every treatment at scheduled treatment visits and record these in the eCRF. The IOP should be carefully monitored by the Investigator for non-transient increases (≥25 mmHg) and treated if necessary as the IVT injection is contraindicated with high IOP. Thirty to 60 minutes after every IVT injection, the IOP should be measured. If it is ≥25 mmHg, it should be remeasured regularly until such time that it is within the normal range. All observed clinical abnormalities should be noted in the AEs page of the eCRF.
- A fundus examination/ophthalmoscopy: This includes an evaluation of the vitreous, retina, macula, choroid, and optic nerve. Dilatation for the fundus examination is at the discretion of the Investigator. This test should be conducted in the study eye by the Investigator at every visit. An examination of the peripheral retina must be conducted to ensure that the IVT injection can be performed safely. Any clinically significant abnormalities observed by the masked Investigator should be recorded on the AEs page of the eCRF.

8.4.2 Post-injection assessment

After the administration of each IVT injection, the study eye will be assessed at 0-5 minutes after the procedure. This assessment includes a gross assessment of vision (e.g. count fingers), the status of the central retinal artery, the presence of retinal detachment, any new intraocular haemorrhage.

If a participant develops a poorly perfused central retinal artery in the study duration, it should be monitored at the Investigator's clinical discretion and expertise; additional procedures and IOP measurements beyond the study protocol can be performed. If the post-treatment assessments are completed and there are no safety concerns after the stipulated time period, the participant is allowed to leave the site. However, in case of any immediate concerns or toxicity, the participant must stay at the site and the designated physician will use his/her clinical expertise to administer treatment. If the participant experiences any IOP issues after the IVT injection, a scheduled follow-up visit can be set up for the next day, at the Investigator's discretion. All clinically important changes noted in the participant after the IVT injection should be noted as AEs. The participants must be instructed to immediately report to the Investigator any symptoms including eye pain, redness of the eye, photophobia, and blurring of vision.

9 Study discontinuation and completion

9.1 Discontinuation

The study treatments can be terminated either by the participant or the Investigator earlier than the planned duration.

Discontinuation of the study treatments for a participant can be the decision of the Investigator or the participants can withdraw their consent. The Investigator may decide to withdraw a participant from the study if he/she believes that continuing the study treatments could negatively impact the participant's well-being. Adequate medical follow-up will be advised for all participants who prematurely discontinue the study for their own reasons or on medical advice from the Investigator.

Participants who prematurely leave the study and/or discontinue study treatments will be replaced where possible.

9.1.1 Study treatment discontinuation

Criteria for discontinuing the study treatment:

- Participant's/guardian's decision
- Pregnancy
- Rescue treatment used in the study eye or prohibited treatments used in the study eye as specified in 6.2.2 Prohibited medication
- Circumstances that will risk the safety of the study participants.

Participants who choose to discontinue the study treatment should be followed up by the Investigator in an effort to understand the participant's reasons for abandoning the study, and this information should be recorded.

When participants withdraw from the study treatment for medical or personal reasons, their withdrawal should NOT be considered final UNTIL they withdraw their consent (see 9.1.2 Withdrawal of informed consent). If possible, they should visit the site for the EOS assessments indicated in the assessment schedule. If they fail to present for these assessments, the Investigator should make a concerted effort (e.g. telephone, email, letter) to get in touch with the participants' pre-designated contact as specified in 9.1.3 Lost to follow-up.

9.1.2 Withdrawal of informed consent

Enrolled participants can voluntarily withdraw their consent from the study for any reason at any time. The criteria for participants' withdrawal of consent are:

- No longer wish to participate in the study,
- No longer permits visits or assessments, and
- No longer wish to have any further study-related contact henceforth.

In case of withdrawal by the participant, the Investigator should try (by telephone, email, letter) to comprehend the main reason for the participant's decision to withdraw his/her consent and make a note of it. There should be cessation of the study treatments and no further assessments should be performed. The conducted assessments and the data that would have been collected at the remaining visits of the planned protocol should be considered missing.

Any contact with the participant from this point onwards is not permitted unless the safety assessments indicate otherwise. It is important to try and perform final assessments before participant withdrawal from the study. The final assessments should be completed as described in Table 4. Assessment schedule. Any

data, information, and analysis of the participant's samples collected during the course of the study before participant withdrawal will be retained and used by the Sponsor.

9.1.3 Lost to follow-up

If participants have not attended scheduled visits without informing the study staff and without clarifying their intent about continuing or withdrawing their participation in the study, the Investigator must follow 'due diligence' by recording the efforts made to communicate with the participant, e.g. dates of telephone calls, registered letters etc. Until all the steps for due diligence have been performed, the participant cannot be considered lost to follow-up.

9.1.4 Early study termination by the Sponsor

It is at the Sponsor's discretion to prematurely terminate the entire study or a particular study site.

Some causes of premature termination are:

- Non-compliance with the protocol by the participant and/or the study site
- Failure on the part of the Investigator to either recruit sufficient participants or enrol participants at the required rate
- Identification of an unanticipated, significant or unacceptable risk for the enrolled study participants
- Unanticipatedly elevated number of AEs
- Advice by relevant boards or committees after a review of the safety and efficacy data.

If the Sponsor decides to terminate the study, the well-being and protection of the participants is the first consideration and participants should be assessed at the earliest for a final visit as if they have prematurely withdrawn. Additional procedures can be added at the Investigator's discretion to safeguard the participants' interests.

9.2 Study completion and post-study treatment

Completion of the study means the EOS for the final participant has been completed and any repeat assessments have been recorded and followed up by the Investigator or, if it is a premature termination of the study, the date of that decision.

There should be a safety follow-up visit scheduled four weeks after the last study treatment administered to each participant. Any information from this visit must be added to the eCRF as source documentation. The Investigator should advise all the participants (and withdrawers) about the correct follow-up for DMO treatment from that point onwards.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events (AEs)

The Investigator(s) will use the National Medical Research Council (2016) safety monitoring and reporting in clinical trials definitions for identifying and coding all the AEs, SAEs, and serious adverse reactions (SARs), and manage participant safety in these incidences. Sponsor-qualified medical personnel will be on hand for advice on medical queries or issues.

After the AEs occur, they must be monitored until resolved, except in circumstances where they are expected to exist for the duration of the study. The AEs will be assessed for progress or response to interventional treatment at each scheduled visit, although additional visits can be organized, if deemed necessary.

10.1.2 Serious adverse events (SAEs) reporting

For the sake of participant safety, any SAEs that occur between completing the PICF and four weeks after the last study treatment should be reported within 24 hours of knowing about the incident, regardless of the cause.

Information about SAEs including the interventions, patient progress, unexpected outcomes, and other follow-up should be noted by the Investigator under the original incidence within 24 hours of knowledge about these developments. If an SAE takes place either at a different time interval or in conditions unrelated to an earlier SAE, it is considered a new event and should be noted as such.

11 Data collection and database management

11.1 Data collection

The participants will be assigned a unique identifying code; this will be put on all documentation and study reports. Clinical data gathered at the study visits will be noted and saved in a customized electronic study database. Information gathered at every study visit will be input into the eCRF in this database unless the database cannot be accessed, in which case data will be transcribed from hard copy (paper) and/or electronic source documents (electronic health records) to the database later. The main study site will include a designated key-locked filing cabinet for safe storage of hard-copy documents related to the study. The electronic study database will have safety guards including password protection with automatic-tracking capability, regular back-ups to a secure cloud-based server and a dedicated physical hard drive.

11.2 Database management and quality control

The completeness and accuracy of the study data collected and entered by the team of Investigators will be scrutinised by Sponsor personnel. The Sponsor will receive the results of the electronic OCT images interpreted by the Investigator. The data management staff will crosscheck the information reported on the eCRF against the data received from the Investigator.

After the information in the database is declared complete and accurate, the database will be secured until the time for data analysis. From that point onwards, any alterations to the information in the database cannot be made without approval from the Sponsor's development management.

11.3 Site monitoring

Before a site initiation visit or an Investigator's meeting before study initiation, the protocol and data recording facilities (i.e. eCRFs) will be examined by a delegated Sponsor representative along with the Investigators and their staff. The Sponsor will utilise varied techniques over the course of the study, to guarantee that protocol and good clinical practice (GCP) compliance, and the quality/integrity of the sites' data is protected. When the field monitor conducts visits, he/she will be assisted by key study personnel who must be available for these visits to the study sites to examine the completeness of participant records, accuracy of data capture/data entry, compliance with the protocol and GCP, adequacy of enrolment, and to check the storage, dispensation and tally of study treatments is conducted as specified.

The information collected for every study participant, including case and visit notes (hospital or clinic medical records) with demographic and medical information, retinal images, test and assessment results, and the original PICF signed by the participant (a signed copy is given to the participant) should be maintained as source documents by the Investigator.

The field monitor must have complete access to the source documents so that the accuracy and consistency of the recorded information in the database and eCRF can be reviewed. The monitoring standards of the Sponsor need complete verification of informed consent, compliance with the inclusion/exclusion criteria, SAEs documentation, and data to be used for all the primary variables.

12 Data analysis and statistical methods

Statistical analysis will be carried out by a trial biostatistician. Data analysis will be performed after all the subjects complete the study. Analysis of the primary endpoint (mean change from baseline in the BCVA at month 12) will be conducted on all the participants' data. Any efficacy and safety data of the participants collected during the study will also be included in the final analysis.

12.1 Analysis sets

The analysis data set comprises all the participants to whom the study treatment has been assigned by randomization, to whom at least one treatment was administered, and for which at least one post-baseline BCVA value is available.

The safety set includes all the participants who received at least one dose of study treatment. The participants will be analysed according to the study treatment received.

12.2 Participant demographics and other baseline characteristics

The demographic and other baseline data, including the disease characteristics will be listed and summarized descriptively by treatment group for each treatment set. Descriptive statistics will be produced for age, BCVA, CMT, and IOP as continuous variables. Relevant medical histories and current medical conditions at baseline will be summarized for all the participants in the treatment groups. The categorical data will be presented as frequencies and percentages. For continuous data, the mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum values will be presented.

12.3 Treatments

The study medication administration will be summarized for all the participants in the treatment set by treatment arm. The subgroup analysis will include regional versus metropolitan participants. Categorical data will be summarized as frequencies and percentages. For continuous data, the mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum values will be presented.

The compliance to treatment protocol will be summarized as the number of injections received per study eye, and the number of attendances per study eye. The participants who had cataract procedures performed during the study will be summarized by number, percentage, and visual outcome.

12.4 Analysis of the primary outcome

12.4.1 Definition of primary endpoint(s)

Non-inferiority is defined as any difference in the BCVA that does not cross the non-inferiority margin of 0.1 LogMAR (1 Snellen line equivalent). The non-inferiority outcome will be presented as the upper bound of the 2-sided 90% CI of the difference in the BCVA and reported in reference to the non-inferiority margin.

12.4.2 Hypothesis and method of analysis

Hypothesis

IVT Ozurdex is non-inferior to IVT Avastin, in terms of visual and macular structural outcomes in Aboriginal patients receiving treatment for centre-involving DMO.

Method of analysis

The Snellen visual acuity measurements will be converted to LogMAR for statistical analysis and reporting. Non-inferiority will be tested using a 1-sided test. The 90% CI of the mean BCVA change from baseline to 12 months difference between the treatment arms will be calculated and the upper bound compared to the

0.1 LogMAR non-inferiority margin. Non-inferiority will be confirmed, if the non-inferiority margin is not exceeded. For all statistical tests, a significance level of 0.05 will be applied.

12.4.3 Handling of missing values

The last-observation-carried-forward method will be used for missing data from missed visits.

12.5 Analysis of secondary outcomes

12.5.1 Efficacy endpoint(s)

- The proportion of participants with a BCVA loss or gain of <0.3 LogMAR ('stable BCVA'), a BCVA loss of ≥0.3 LogMAR ('decline in BCVA'), and a BCVA gain of ≥0.3 LogMAR ('gain in BCVA') will be calculated.
- The change in the CMT will be calculated from baseline to 12 months.
- The descriptive statistics of the mean number of injections, and attendances will be calculated for each group.
- The calculated IOP outcomes will include the change in mean IOP, the number of participants with one or more occasions of IOP elevation >28 mmHg, an increase in IOP by >10 mmHg from baseline to 12 months, and IOP elevations requiring medical, laser or surgical treatment.

12.5.2 Safety endpoints

Safety summaries will include:

- AEs and SAEs
- Ophthalmic examinations
- Post-injection assessments

Safety summaries (tables, figures) only include data from the treatment period. The treatment period lasts from the date of the first administration of the study treatment to 1 month after the date of the last actual administration of either study treatment.

12.5.3 Supplementary analysis

The influence of cataract surgery during the trial on the treatment effect will be analysed using covariance analysis (ordinary least squares regression), and an analysis of the mean change in the pre- versus post-operative BCVA in patients who had cataract surgery. Subanalyses will be carried out for metropolitan versus regional participants for all of the above analyses.

12.6 Sample size calculation

This study aims to recruit 50 patients. The patients will be recruited over a 12-24 month period and followed for 12 months. The sample size calculation was performed with assistance from an Allergan statistical consultation in December 2017, with the following assumptions:

Non-inferiority margin: 20%; study power: 0.80; level of significance: 0.05

Treatment effect (responder rate) in each group: 0.80

The sample size for determining 80% power of non-inferiority by excluding a difference in the mean change in BCVA between the treatment arms of 20% (equivalent to 0.1 LogMAR, or 1 line of Snellen visual acuity), with a 1-sided alpha significance level of 0.05%, was calculated to be 50 eyes.

The subjects who withdraw prematurely will be replaced where possible.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

The protocol for this study has been planned following the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007), and the ethical principles from the World Medical Association Declaration of Helsinki.

13.2 Publication of the study protocol and results

The protocol for this study will be registered in a public database, e.g. the Australian New Zealand Clinical Trials Registry (ANZCRT) or clinicaltrials.gov. Upon completing this study, the outcomes of this investigation are intended for publication in a peer-reviewed journal.

14 Protocol adherence

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

The Investigators ascertain that they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study, this must be considered a protocol amendment, and unless such an amendment is agreed upon by the Sponsor and approved by the Ethics Committee and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Sponsor, Ethics Committee, and Health Authorities where required, prior to its implementation.

Only the amendments required for participant safety may be implemented immediately, provided the Health Authorities and the reviewing Ethics Committee are subsequently notified by protocol amendment.

Notwithstanding the need for the approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, the Sponsor should be notified of this action.

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16 Appendices

Flowchart