**PHASE 1 SAFETY AND TOLERABILITY TRIAL OF LEVODOPA EYE DROPS FOR THE TREATMENT OF MYOPIA**

**UNIVERSITY OF CANBERRA**

| Study design                  | Monocentre, phase I first-in-human, placebo controlled, double-blind, randomised, paired-eye, multi-dose, safety and tolerability trial. |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| Intervention                 | Low (1.4 levodopa:0.34 carbidopa (µmoles/day)) or standard dose (2.7 levodopa:0.68 carbidopa (µmoles/day)) of levodopa/carbidopa eye drops. |
| Duration of study            | Four weeks with a four-month follow-up                                                                                           |
| Sponsor                      | University of Canberra, Australia                                                                                                 |
| Study centre                 | University of Canberra Eye Clinic, Australia                                                                                       |
| Principal investigator       | Associate Professor Regan Ashby                                                                                                   |
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| Funding                      | University of Canberra – Internal Funding  
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STUDY PROTOCOL

STATEMENT OF COMPLIANCE

This trial was designed in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice (GCP) and guideline M3 adopted by the Australian Clinical Trial Handbook (ACTH). This study will be undertaken under the Therapeutic Goods Administration (TGA) Clinical Trial Notification scheme (CT2020-CTN-04134-1-v1), and is registered with the Australian New Zealand Clinical Trial Register (ANZCTR; ACTRN12620001259932). This study will adhere to the CONSORT statement, tenets of the Declaration of Helsinki and has been approved by the University of Canberra Human Ethics Committee (HREC-0406).

PROTOCOL SUMMARY

Synopsis

One of the earliest and most consistent biochemical changes implicated in animal models of myopia is a reduction in retinal dopamine release [for review see 1]. If this dysregulation of the dopaminergic system is a universal requirement for excessive growth, restoring dopamine levels may form an effective clinical treatment for myopia in humans. Therefore, our group has reformulated the dopamine precursor levodopa and a bioavailability enhancer, carbidopa, into a topical ophthalmic solution for direct application to the eye. In animals, this topical levodopa/carbidopa treatment abolishes experimental myopia, shows minimal systemic distribution, and does not alter normal ocular development or ocular health over long-term treatment periods 2,3. To examine the safety profile of this topical formulation further, this study describes a Phase I first-in-human monocentre, placebo controlled, double-blind, randomised, paired-eye, multi-dose safety and tolerability trial in young healthy adults (males, 18-30 y/o, mean age 24.9 ± 2.7 years) treated once a day for a period of four weeks (28 days).
## Schedule of activities

| Visit schedule                              | Baseline/screening | Week 1 | Week 2 | Week 3 | Week 4 | Follow-up |
|---------------------------------------------|--------------------|--------|--------|--------|--------|-----------|
| Screening questionnaire                      | x                  |        |        |        |        |           |
| Drug Treatment                               | x                  | x      | x      | x      | x      |           |
| Dispensing of treatment dropper bottles      | x                  | x      | x      | x      | x      |           |
| Dominant eye test                            | x                  |        |        |        |        |           |
| OSDI questionnaire                           | x                  | x      | x      | x      | x      | x         |
| Corneal staining                             | x                  | x      | x      | x      | x      |           |
| Conjunctival staining                        | x                  | x      | x      | x      | x      | x         |
| Tear film break-up time                      | x                  | x      | x      | x      | x      | x         |
| Tear film osmolarity                         | x                  |        |        |        |        |           |
| High contrast visual acuity                  | x                  | x      | x      | x      | x      | x         |
| Low contrast visual acuity                   | x                  | x      | x      | x      | x      |           |
| Multifocal electroretinogram                 | x                  |        |        |        |        |           |
| FDT perimetry                                | x                  |        |        |        |        |           |
| Optical coherence tomography                 | x                  | x      | x      | x      | x      | x         |
| Intraocular pressure                         | x                  | x      | x      | x      | x      | x         |
| Fundus photography                           | x                  |        |        |        |        |           |
| Cycloplegic autorefraction                   | x                  |        |        |        |        |           |
| Ocular biometry                              | x                  | x      | x      | x      | x      | x         |
| Amplitude of accommodation                   | x                  | x      | x      | x      | x      | x         |

## ABBREVIATIONS

- **AAAD**: Aromatic amino acid decarboxylase
- **ACTH**: Australian Clinical Trial Handbook
- **AMD**: Age-related macular degeneration
- **ANZCTR**: Australian New Zealand Clinical Trial Register
- **AR**: Adverse reaction
- **CIOMS**: Council for International Organizations of Medical Sciences
- **CTC**: Clinical Trial Coordinator
- **CTN**: Clinical Trial Notification Scheme
| Acronym | Full Form |
|---------|-----------|
| EDI     | Enhanced depth imaging |
| ETDRS   | Early treatment of diabetic retinopathy study |
| FDT     | Frequency Doubling Technology |
| GCP     | Good Clinical Practice |
| GMP     | Good Manufacturing Practise |
| HREC    | Human Research Ethics Committee |
| ISCEV   | International Society for Clinical Electrophysiology of Vision |
| ICH     | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IOP     | Intraocular pressure |
| mfERG   | Multifocal electroretinogram |
| NEI     | National Eye Institute |
| NHMRC   | National Health and Medical Research Council |
| OCT     | Ocular coherence tomography |
| OSDI    | Ocular Surface Disease Index |
| PETE    | Polyethylene terephthalate |
| RAF     | Royal Air Force |
| SUSAR   | Suspected unexpected serious adverse reactions |
| TGA     | Therapeutic Goods Administration |
| UC      | University of Canberra |
| USM     | Urgent safety measure |
| VA      | Visual acuity |
INTRODUCTION

Study rationale

In preclinical studies, levodopa/carbidopa eye drops appear to be a promising novel intervention for the treatment of myopia (short-sightedness). To examine the safety profile of this topical formulation before moving to patient efficacy trials, this study describes a Phase I first-in-human monocentre, placebo controlled, double-blind, randomised, paired-eye, multi-dose safety and tolerability trial in young healthy adult males (18-30 y/o) treated once a day for a period of four weeks.

Background

This protocol describes a first-in-human safety and tolerability trial for a novel ophthalmic treatment for the leading cause of visual impairment and low-vision worldwide (myopia)\(^4\). The refractive disorder myopia (short-sightedness) is a chronic progressive condition arising from excessive growth of the eye during development\(^5\). Although the visual blur associated with myopia can be easily corrected by glasses, contact lenses or laser surgery, this does not address the sight-threatening pathological changes associated with excessive growth of the eye during myopia development (e.g., retinal detachment, myopic maculopathies, and staphyloma, as well as an increased risk of glaucoma and cataracts)\(^6\). The odds of developing such pathologies increase with the severity of myopia\(^7\). The public health and financial returns to be obtained through myopia prevention are significant. Therefore, the field continues to investigate and develop novel interventions for myopia to enhance patient outcomes. This study will investigate one such potential intervention, which targets the retinal dopamine system.

One of the earliest and most consistent molecular changes implicated in the development of experimental myopia in animal models is dysregulation of the dopamine system within the eye\(^8-10\). Specifically, retinal levels of dopamine are significantly reduced during the development of experimental myopia in all species studied\(^1\). In agreement with a role for dopamine in ocular growth regulation, stimulation of the dopaminergic system by ocular administration of the natural ligand (dopamine), a dopaminergic mimic (agonists), or the dopamine precursor levodopa, can abolish the development of experimental myopia\(^1-3,11\). While most of this dopaminergic pathway evidence comes from studies in animal models, systemic administration of the dopamine reuptake inhibitor methylphenidate has recently been reported to inhibit myopia development in children with attention deficit hyperactivity disorder\(^12\). If this dysregulation of the dopaminergic system is a universal requirement for excessive growth, restoring dopamine levels may form an effective clinical treatment for myopia in humans.

Based on this association, our group has reformulated the drug levodopa (L-DOPA) into an ophthalmic solution for the treatment of myopia. Levodopa, the precursor molecule to dopamine, has been in clinical use for over five decades for the treatment of neurological disorders involving diminished dopamine levels, such as Parkinson’s disease\(^13\). For such disorders, levodopa is administered systemically as a tablet. A major disadvantage of such systemic treatment is the extensive decarboxylation of levodopa to dopamine in peripheral tissue by aromatic amino acid decarboxylase (AAAD), allowing only a small percentage of the oral dose to reach the brain\(^14,15\). This is commonly overcome by co-administering levodopa with a peripheral AAAD inhibitor such as carbidopa\(^15\). In the case of myopia, the systemic administration and distribution of
levodopa is not appropriate due to unwanted distribution to the brain. Therefore, we have reformulated levodopa into a topical solution that can be directly applied as eye drops.

In animal models, an ophthalmic levodopa/carbidopa solution can prevent the onset and progression of experimental myopia in a dose-dependent manner, abolishing the development of myopia at higher doses (for a full pre-clinical dataset, see 2, 3, 11). Importantly, a comprehensive analysis of the short- and long-term ocular safety of levodopa/carbidopa eye drops in an avian (chicken) and mammalian (mouse) model (for a full pre-clinical dataset, see 2, 3, 11) observed no adverse effects in preclinical testing. Specifically, the effects of levodopa and levodopa/carbidopa eye drops on ocular health have been tested over a 9-month treatment period using standardised clinical measures, including - visual function (electroretinogram), retinal health (histology), intraocular pressure (IOP) and ocular development (axial length and refraction). No adverse changes were observed for each of these measures 2. These findings mirror those reported from Parkinsonian patients, in which levodopa treatment does not alter normal visual function, even at concentrations well above those needed for the treatment of myopia 16-21.

These preclinical safety and toxicity studies undertaken in animal models also suggest that levodopa/carbidopa eye drops do not induce any systemic side effects. However, as there is currently no clinical data available on the use of topical levodopa, in ophthalmic preparations or elsewhere, it is difficult to evaluate the degree to which levodopa eye drops may induce side effects in humans. In otherwise healthy children and young adults, side effects from systemic levodopa treatment can include headaches, nausea, fatigue, mood changes, nightmares, emesis, dizziness, dry mouth, and decreased appetite 22. However, during its systemic use in humans, levodopa is administered at doses well above those which will be used for the treatment of myopia. Therefore, the side effects listed above, which will only occur if levodopa is systemically distributed, are much less likely to occur in this study due to both the dose and route of administration used.

Together, preclinical findings from animal models indicate that levodopa may be a powerful therapeutic solution for myopia. Prior to testing in a patient population, ocular safety and tolerability of levodopa/carbidopa eye drops must be established in humans. This will complement the preclinical safety findings from animal models.

**Risk/benefit assessment**

This ophthalmic solution is categorised as low risk based on the significant safety data from animal models and the substantial safety data pertaining to the systemic administration of levodopa/carbidopa in humans at the dosages being proposed for this study (see above). According to the National Health and Medical Research Council (NHMRC) guidance for Risk-based Management and Monitoring of Clinical Trials Involving Therapeutic Goods, this formulation of levodopa falls into the Type B risk category, in which an existing product on the Australian Register of Therapeutic Goods is modified or used for a new indication.

The risk associated with the conducting of this trial, which has been purposely designed with a minimal level of complexity, is also low. The topical solution has been formulated to avoid any known discomforts associated with topical solutions (i.e., the use of certain preservatives, as well as pH levels) and has been shown to have a high level of tolerability in animal models with no observed side-effects over treatment periods well beyond the length of this current trial. Participants will be made aware that this topical form of levodopa/carbidopa has not previously been tested on humans.
To minimise any unknown risks on pregnancy, only males aged 18-30 will be enrolled in the study. Also, due to previously reported complications of systemic levodopa, participants will be excluded if: they are currently using, or have used in the past two weeks, monoamine oxidase inhibitors; have a history of melanoma or undiagnosed suspicious skin lesions; have hepatic or renal impairment; have narrow angle glaucoma; or if they have a known hypersensitivity to any component of the medication.

All data will be de-identified and kept on a secure server to which only the clinical trial coordinator (CTC) and sponsor (University of Canberra (UC)) will have access to, thus preventing privacy breaches and the release of health data that could lead to unintended stress for participants.

Potential side effects
Pre-clinical safety and toxicity studies undertaken in animal models have found no ocular or systemic side-effects associated with topical levodopa treatment. With regards to human safety data, levodopa’s use in tablet form in children with amblyopia, at doses much higher (~30 fold) than those that will be used in this study, has been associated in a small percentage of cases with the following potential side effects – headaches, nausea, fatigue, mood changes, nightmares, emesis, dizziness, dry mouth, and decreased appetite 52. Other side-effects that have been reported during systemic levodopa use, such as muscle pain, numbness/tingling, trouble sleeping, increased compulsive behaviours, dyskinesia and other movement disorders, appear to be associated with the disease state being treated (e.g., Parkinson’s disease). No known ocular complications have been reported with the use of levodopa orally.

STUDY DESIGN

Overall design
This first-in-human placebo controlled, monocentre, multi-dose, double-blind, paired-eye randomised clinical trial of topical levodopa/carbidopa will be conducted at the UC Eye Clinic, Australia. Over a 4 week period (from June to July 2021), this study will assess the safety and tolerability of daily treatment to the eye with a topical ophthalmic levodopa/carbidopa solution in healthy young adult males. A post-treatment follow-up will be completed in November 2021, four months following treatment cessation. Participants will be recruited and assigned to receive either a low (1.4 levodopa:0.34 carbidopa (µmoles/day)) or standard dose (2.7 levodopa:0.68 carbidopa (µmoles/day)) of levodopa/carbidopa eye drops in one eye and placebo (vehicle solution consisting of 0.1% w/v ascorbic acid and 0.001% w/v benzalkonium chloride dissolved in 1x phosphate-buffered saline) in the fellow eye (Table S1). Participants will be randomly assigned to either treatment arm, with which eye to be treated, and which eye to act as a control also randomised.

Study outcomes/endpoints
The primary outcome of this trial is to determine the safety and tolerability of levodopa/carbidopa eye drops as assessed by the presence or absence of clinically significant changes in ocular surface tolerability and integrity, visual function, ocular health, and refraction and biometry, as well as the occurrence of drug-related adverse events.
STUDY POPULATION

Inclusion and exclusion criteria
Participants will be enrolled based on the inclusion criteria summarised in Table S2, which will be evaluated at the baseline/screening visit to the UC Eye Clinic.

Strategies for recruitment and retention
Following a recruitment campaign, in which hardcopy posters/flyers will be placed on noticeboards around the University campus and distributed to private optometry clinics in the area, participants will be enrolled between February and June 2021.

To assist in recruitment and retention, in accordance with the NHMRC guidelines for payment of participants in research, participants will be financially recompensed for their travel and parking when attending each visit to the UC Eye Clinic.

STUDY INTERVENTION

Measures to minimise bias: randomisation and blinding
Using an electronic randomisation program, eligible participants will be randomly allocated into the two intervention groups by the lead investigator: (1) those receiving the low-dose ophthalmic solution in one eye and the placebo solution in the fellow eye and (2) those receiving the standard-dose ophthalmic solution in one eye and the placebo solution in the fellow eye. Within each of these groups, the use of the levodopa/carbidopa compound will be further randomised between left and right eyes and the participants’ dominant and non-dominant eyes. The levodopa/carbidopa and placebo eye drops will be packaged in sequentially numbered identical bottles (labelled for administration to the left or right eye). The master list will be held by UC, allowing the participants and all other trial investigators to remain masked in order to minimise treatment and observational bias.

Study intervention and administration
As stated above, participants will be assigned to receive either a low (2.7 levodopa:0.68 carbidopa (µmoles/day)) or standard dose (5.4 levodopa:1.36 carbidopa (µmoles/day)) of levodopa/carbidopa eye drops in one eye and placebo (vehicle solution consisting of 0.1% w/v ascorbic acid and 0.001% w/v benzalkonium chloride dissolved in 1x phosphate-buffered saline) in the fellow eye (Table S1). At each clinical visit over the trial, participants will be given a new set of dropper vials and will be instructed to instil two drops to each eye every morning for the duration of the trial. For optimal protection, participants will be asked to store these vials in the fridge.
Study intervention compliance

Treatment compliance will be monitored via participant interview, diaries distributed to participants to record their eye drop administration and weighing of dropper vials before and after each week of patient use.

Preparation/handling/storage/accountability

The procurement, manufacture, and supply of levodopa/carbidopa as a good manufacturing practise (GMP) certified ophthalmic solution will be undertaken by PCI Pharma Services Pty. Ltd. (Port Melbourne, Victoria, Australia; Licence number: MI-2013-LI-07674-1, Manufacturer ID: 50963). All active compounds will be dissolved in a saline solution, pH 6.0, before being placed in single-use, light-protected polyethylene terephthalate (PETE) plastic dropper. Vials will be transported refrigerated to the test site (UC Eye Clinic). All vials will be stored in locked fridges at the clinical site before distribution to participants. For optimal protection, participants will be asked to store unused vials in the fridge.

Participants will receive one pouch containing two dropper vials to be kept at 4°C, with one vial containing the solution for the left eye and the other for the right eye. According to GCP guidelines (Section 5.13), the pouch will contain the following information: the name, address and contact number of the CTC and sponsor (UC). The CTC will be listed as the point of contact for product and trial information, as well as emergency unblinding procedures (in case of adverse events). The pouch and vials will also clearly state that the solution is for the left or right eye only. The pouch will also detail the potential dosage; route of administration; the batch and/or code number to identify the contents and packaging operation; the trial reference code; the subject’s identification number; the directions for use (i.e., “Administer one drop to the left (or right) eye daily”); “For clinical trial use only”; “May contain levodopa up to an amount of 0.5mg and carbidopa up to an amount of 0.13mg”; the storage conditions (“Keep refrigerated”); the period of use (use by/expiry dates); “Keep out of reach of children”. Each vial will contain the following information: CTC name and contact details for information regarding the product/clinical trial; Route of administration (“Eye drop - left (or right) eye only”); the batch and/or code number to identify the contents and packaging operation; the trial reference code; the subject’s identification number.

Concomitant therapy

Participants will be excluded from the study if they are currently using, or have used in the past two weeks, any of the medications listed in Table S2.
STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT WITHDRAWAL

Participant discontinuation/withdrawal from the study

As part of the informed consent process (see appendix), participants will be informed about their right to withdraw from the study at any time. Participants will also be informed that withdrawal from the study will have no implications regarding their future eyecare, clinical treatment or education.

Participants may also be withdrawn from the study if they experience an adverse event. If a participant withdraws from the study, the trial team will counsel them and encourage them to attend the clinic for an ocular safety screen after discontinuing treatment.

Unless patients ask to retract their data/information, it will be included for analysis provided they have attended one clinical visit following the commencement of treatment. Participants will be able to withdraw their data up until the point that the final outcome measures are collected at which stage re-identifiable data will be anonymised.

Lost to follow-up

A participant will be considered lost to follow-up if they do not attend the 4-month follow-up measures.

Contact measures

The following actions will be taken before a participant withdraws or is deemed lost to follow-up:

- The trial team will attempt to contact the participant and reschedule the follow-up visit within 2-4 weeks of their original appointment.
- The trial team will attempt to counsel the participant on the importance of attending the follow-up visit.
- The trial team will attempt to contact the participant a minimum of 3 times (via phone, email, or text message).
- If the participant remains uncontactable or unwilling to participate further, he will be deemed lost to follow-up.
STUDY ASSESSMENTS AND PROCEDURES

Safety assessments
The safety and tolerability of levodopa/carbidopa eye drops will be measured by evaluating whether treatment induces any clinically significant changes in ocular surface tolerability and integrity, visual function, ocular health, and refraction and biometry, or whether treatment induces any additional adverse events. All eligible participants will undergo the full examination procedure at baseline, end of treatment (4 weeks) and during follow-up (4 months) to determine the safety of levodopa/carbidopa (these will be referred to as the primary measurement points). A subset of these measures will also be collected each week during the 4-week treatment period (referred to as the secondary measurement points). The well-defined clinical measures used to assess the safety and tolerability of the topical ophthalmic drops are outlined below and summarised in Table S3.

Measures of ocular tolerability and anterior surface integrity
Dry eye symptomology will be assessed using the validated Ocular Surface Disease Index (OSDI) questionnaire (Allergan Inc., Dublin, Ireland) at primary and secondary measurement points. Corneal and conjunctival epithelial integrity will be evaluated at primary and secondary measurement points by applying sodium fluorescein to the bulbar conjunctiva using a wetted fluorescein strip. As previously described, corneal (divided into 5 sectors) and conjunctival (divided into 6 sectors) epithelial desiccation will be graded on a 0-3 scale using the National Eye Institute (NEI) grading scale.

Following conjunctival and corneal epithelial grading, fluorescein break-up time will be evaluated at each visit. If required, sodium fluorescein will be reapplied to the bulbar conjunctiva. Following standard procedures, participants will then be asked to blink naturally three times before the clinician monitors the tear film for the first sign of a disruption.

Participants will also have their tear film osmolarity assessed using the TearLab Osmolarity System (TearLab, California, USA) at primary measurement points (baseline, end of treatment (4 weeks) and follow-up (4 months)). Following standard procedures, the tear lab test card will be gently touched to the inferior lateral meniscus of the tear film above the lower eyelid to collect approximately 50 nL of tear fluid, which will then be read by the factory calibrated osmolarity system.

Measures of visual function
Multifocal electroretinogram (mfERG) recordings will be used as the primary measure of visual function and will be assessed at the primary measurement points (baseline, end of treatment (4 weeks) and follow-up (4 months)). Both scotopic and photopic mfERG will be measured following the International Society for Clinical Electrophysiology of Vision (ISCEV) mfERG protocol. The mfERG stimulations will be performed using a Visual Evoked Response Imaging System (VERIS 5.1.5x refraactor/camera system, Electro-Diagnostic Imaging Inc., Redwood City, California, USA) under mesopic room conditions (approximately 300 cd/m²). mfERGs will be recorded 35 minutes after the induction of cycloplegia and pupil dilation (using 1.0% cyclopentolate and 2.5% phenylephrine administered 5 minutes apart).
Gross changes in foveal visual function will be further evaluated at both primary and secondary measurement points via standard clinical measures of high (>90%) and low (10%) contrast visual acuity (VA; Hi-Low contrast logMAR chart, Australian College of Optometry, Carlton, Victoria, Australia) 28. Additionally, at the primary measurement points all participants will undertake a 10-2 threshold strategy (central 20-degree) visual field test using Frequency Doubling Technology (FDT) perimetry (Matrix, Carl Zeiss Meditech, Dublin CA) to subjectively measure the overall function of the visual pathway. The Matrix perimetry will be undertaken as previously performed by Anderson and colleagues 29, with all results compared to a predefined normative database in the software.

Assessment of ocular health

Retinal structure, total retinal thickness, retinal nerve fibre layer thickness, and sub-foveal choroidal thickness will be assessed at primary and secondary measurement points by enhanced depth imaging (EDI) ocular coherence tomography (OCT) (Spectralis, HRA + OCT; Heidelberg Engineering, Heidelberg, Germany, software version 6.9.5.0). For OCT analysis, two scans will be obtained for each subject: a posterior pole scan (P-Pole) centred on the fovea (24° x 24°) and a retinal nerve fibre scan centred on the optic disc (12° in diameter). In the first scan, retinal thickness will be defined automatically by the Spectralis software in an 8x8 grid, while sub-foveal choroidal thickness will be defined manually in the OCT software as the distance between the two choroidal borders (from the outer edge of the retinal pigment epithelium (marked by the hyperreflective line) to the inner surface of the sclera). Autofluorescence of images from the Spectralis will be visually analysed by clinicians at each primary measurement point (baseline, end of treatment, and at follow-up) for the occurrence of hyper- or hypo-fluorescent lesions as discussed by Yung and colleagues 30.

At primary measurement points, digital retinal imaging will also be conducted on all subjects using Wide-field fundus colour photography (Clarus 500, Carl Zeiss Meditec, Dublin, CA). Fundus photographs will be assessed for signs of pathology (e.g., haemorrhage/microaneurysms, exudates, neovascularisation) by a certified clinician using the early treatment of diabetic retinopathy study (ETDRS) grading system 31, 32.

As systemic levodopa is historically contraindicated in patients with narrow anterior chamber angles, IOP will be assessed at both primary and secondary measurement points using rebound tonometry (iCare ic100) as described by Fernandes and colleagues 33.

Assessment of refractive error and ocular biometry

Changes in spherical equivalent refraction will be measured by cycloplegic autorefraction (achieved by administering one drop each of 1.0% cyclopentolate and 2.5% phentolamine to each eye) at baseline, treatment cessation, and follow-up. Cycloplegic auto-refraction will be measured objectively with an autorefractor (Nidek Tonoref III; Gamagori, Japan) three times to obtain a mean value.

Ocular biometry (axial length, corneal thickness, anterior chamber depth and corneal curvature) will be measured at each clinical visit using low coherence interferometry (Lenstar, Haag Streit, USA). Following the procedures outlined by Cruysberg and colleagues 34, participants will be asked to focus on a target to ensure all measurements are taken on the visual axis and five consecutive measurements will be taken per eye.

Monocular amplitude of accommodation will be measured at each clinical visit using a Royal Air Force (RAF) rule. The near point of accommodation will be determined, in dioptres, by measuring the nearest distance to the participant at which the smallest letter on the RAF rule target remains in focus.
Adverse events and serious adverse events

Definition of adverse events

An Adverse Event (or adverse reaction (AR)) will be classified as any untoward or unexpected medical occurrence, disease, injury or clinical signs observed by the clinical team or reported by participants during or after the study.

Definition of serious adverse events

A Serious Adverse Event (or suspected unexpected serious adverse reactions (SUSAR)) will be classified as an adverse event that:

- Leads to a death, or;
- Leads to a serious deterioration in health that:
  - Results in a life-threatening illness or injury;
  - Results in a permanent impairment of body structure or function;
  - Requires hospitalisation;
  - Results in medical or surgical intervention to prevent illness or injury.

Adverse event reporting

Adverse events and/or reactions will be reported by the investigating team to the sponsor (UC), CTC and lead investigator within 24 hours. The sponsor, in conjunction with the CTC and lead investigator, will report such events to the human research ethics committee (HREC) in its annual safety report which will include: a description and analysis of new and relevant findings, an analysis of its current safety profile and its implications, the trial’s risk-benefit ratio, and any measures taken or proposed to minimise risks.

All serious adverse reactions and/or events will be reported by the investigating team using a blue card or Council for International Organizations of Medical Sciences (CIOMS) 1 form to the sponsor, CTC and lead investigator within 24 hours. The sponsor, in conjunction with the CTC and lead investigator, will report such events to the HREC in its annual safety report. Furthermore, for SUSARs, the sponsor and CTC will break the blinding, whilst maintaining it for all other parties involved in the management, conduct, or analysis of the trial, and immediately inform the institute’s HREC and the TGA. Significant safety issues (which can include serious adverse reactions/events not classified as SUSARs or any safety issue requiring action) will be reported by the investigators to the sponsor, CTC and lead investigator within 72 hours, who will then report to the HREC and TGA within 15 days. Should these issues require an urgent safety measure (USM) to be undertaken, the sponsor will report to the HREC and the TGA within 72 hours. Any amendments to the protocol or halts/early terminations of the study will be reported to the HREC and the TGA within 15 days. For all suspected adverse events, the clinical team and CTC will immediately refer the participant for an independent assessment by an Ophthalmologist for evaluation and management.
STATISTICAL CONSIDERATIONS

Sample size determination
Assuming a dropout rate of 15-20%, a sample size of 14-15 was calculated, using the equation below, to be required for each treatment group in this study.

\[ n_1 = \frac{\left(\sigma_1^2 + \sigma_2^2 / K\right)\left(z_{1-\alpha/2} + z_{1-\beta}\right)^2}{\Delta^2} \]

In which: \( \Delta \) = absolute difference between two means; \( \sigma_1, \sigma_2 \) = variance of mean #1 and #2; \( n_1 \) = sample size for group #1; \( \alpha \) = probability of type I error (0.05); \( \beta \) = probability of type II error (0.1); \( z \) = critical Z value for a given \( \alpha \) or \( \beta \); \( k \) = ratio of sample size for group #2 to group #1.

This was based on a power calculation undertaken for one measure each for ocular surface tolerability and integrity, visual function, ocular health, and refraction/biometry. These power calculations determined that a minimum sample size of 12 participants would be required per group (assuming a type 1 error of 5% (two tailed) and a power of 90%) to detect a meaningful difference of 13.4 in the ocular surface disease index, 1.5 milliseconds in mfERG oscillation potentials, and a 20% change (60 µm) in retinal thickness.

Statistical analyses
Data from all participants who complete at least one measurement point following the commencement of treatment, whether they complete the trial or not, will be included in the statistical analysis. Changes in measures of ocular tolerability and anterior surface integrity, visual function, ocular health, as well as refraction and ocular biometry will be analysed via a linear-mixed effects model adjusted for repeated measures. Using the restricted maximum likelihood method, this mixed effects model will study the effects of time, treatment (placebo versus low dose levodopa/carbidopa versus standard dose levodopa/carbidopa) and the interactions between time and treatment on an intention-to-treat principle. Random effects in the model will include the subject effects (within-subject variability and errors). Treatment effects at selected time points will be calculated by constructing estimates from all actual observations of the treatment effects at that time, combined with contributions from the observations at other times, with no attempt at imputation or adjustment for missing data. Following this, treatment groups will be compared across the different timepoints using a Tukey’s correction for multiple comparisons. Data will be analysed using GraphPad Prism v9.3.1 and Matlab (2020b Mathworks Inc., Natick, MA).
ADDITIONAL CONSIDERATIONS

Oversight and monitoring
The CTC will be allocated to be responsible for:

- The recruitment and enrolment of participants;
- The coordination and the running of the trial;
- The allocation of participants to the specific trial arms, using a centralised electronic randomisation system, and maintenance of the master randomization list of participants;
- The dispensing of the ophthalmic solution;
- Implementation of study-specific clinical monitoring tools and documents including the ocular tolerance questionnaire;
- The implementation and adherence to clinical trial and academic research protocols;
- The recording of adverse event and side effect information, and consultation with investigators concerning the reporting of events to regulatory agencies;
- Reporting actual and potential adverse events and Serious Adverse Events;
- Management of clinical data and ensuring patient privacy;
- Overseeing and/or coordinating the collection, handling, analysis and reporting of patient and trial data.

Data handling and record keeping
Information that is re-identifiable will be coded (via a code key) by a member of the team not involved in trial measures. The code key and data will be stored separately, and the code key will be destroyed when all data has been collected and matched. Hard copies of trial data will be stored at UC, while digital records will be stored on the University server. Data will only be accessible to the investigatory team and sponsor, with the list of authorised personnel to be kept with the sponsor. The investigatory team will have read-only access to submitted data, with changes to the data only available to a designated member who is not involved in the collection of data and does not hold any commercial interest in the product, with an audit trail to be maintained to ensure the original data are always accessible. Blinded data entry will be maintained throughout entry and processing, with treatment allocations remaining separate on the master randomisation list.

Following trial completion, data will be retained by the sponsor. Digital data will be stored behind the firewall on the UC server, while hard copies of the trial data will be deidentified and stored in a locked filing cabinet in a secure facility. Data will be accessible only by the authorised parties for at least 5-years following the last approval of a marketing application or formal discontinuation of the product.

Publication and data sharing policy
This trial will be undertaken under the Clinical Trial Notification scheme (CT2020-CTN-04134-1-v1), and is registered with the Australian New Zealand Clinical Trial Register (ANZCTR; ACTRN12620001259932).

To ensure that the study results are publicly disseminated, the trial team will submit their findings as a manuscript for peer-review within 2 years following the completion of this study.
Conflict of interest policy

The primary investigator has lodged an international patent application pertaining to the compounds to be tested (PCT/AU2017/050310). To prevent the potential for compromised judgement or perceived bias, the primary investigator will not undertake any of the measures associated with testing the ocular safety and tolerability of this compound. This will instead be undertaken by our team of clinically certified optometrists, who hold no commercial interest in the product, under the guidance of the CTC. All data will be analysed by the CTC and clinical team without input from the primary investigator, with the clinical team masked to the treatment of each participant. The primary investigator will not be involved in the manufacture or distribution of the compound for testing. The compound will instead be produced and shipped to the University by PCI Pharma Services Pty. Ltd. (Port Melbourne, Victoria, Australia; License number: MI-2013-LI-07674-1; Manufacturer ID: 50963) and dispensed by the clinical team.
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APPENDIX – EXAMPLE CONSENT FORM

Consent form information bulletin

WHAT IS THE PURPOSE OF THIS TRIAL?

This trial aims to investigate the safety and tolerability of levodopa/carbidopa eye drops, a novel intervention designed to prevent the onset and progression of myopia (short-sightedness).

WHAT TREATMENTS WILL PARTICIPANTS RECEIVE?

Participants will be randomly allocated to one of two equally sized groups:

1. Low concentration levodopa/carbidopa eye drops to one eye and placebo (saline) control drops to the other eye.

2. Normal concentration levodopa/carbidopa eye drops to one eye and placebo control drops to the other eye.

WHAT TYPE OF HEALTH TESTS WILL EACH PARTICIPANT UNDERGO?

During the study we will be assessing routine clinical measures of vision and eye health. Each of your primary visits to the clinic will take approximately 75 minutes. These visits will involve the use of eye drops as a local anaesthetic with a second set of drops used to dilate the pupil which will mean you will be unable to drive for 2-3 hours after the appointment.

These measures of vision and eye health will be undertaken at the following times:

• Before starting the drops;

• The day after stopping the drops (day 29); and

• Three and six months after finishing the drops.

We will also be assessing a smaller subset of measurements at the end of weeks 1, 2, and 3 of the trial. These mid-trial visits will take approximately 30 minutes and will not require the use of eye drops to dilate the pupil and as such you can drive immediately after your clinical visit.

The primary and secondary measures will include:

• Ocular Surface Disease Index (OSDI) questionnaire: this questionnaire will determine the degree of ocular irritation (if any) experienced by participants.

• Visual Acuity: this will test how well participants can see shapes and details.
• Amplitude of Accommodation: this will test how easily participants can view nearby objects.

• Tear Film osmolarity/ break up time: this measures whether there are any changes in the tear composition.

• Anterior Segment Examination (with and without corneal staining): this will measure if there are any changes to the surface of the eye. The corneal stain is applied as eye drops and will wear off during the examination.

• Intraocular pressure (IOP): this measures the pressure within the eye.

• Fundus colour photography: this technique looks through the pupil to examine the eye’s interior.

• Optical Coherence Tomography (OCT): this looks at the structure of the eye’s neural layer (retina).

• Biometry: this measures the length and thickness of all interior components of the eye.

• Auto-refraction and keratometry: this determines if you have a refractive error (i.e., need glasses).

• Multifocal electroretinogram (mfERG): this measures retinal function. For these measurements, thin wire probes will be placed on the surface of the eye. A local anaesthetic will be used to minimise discomfort.

WHAT ARE THE RESPONSIBILITIES OF THE PARTICIPANTS?

Participants will be asked to visit the University of Canberra Eye Clinic before starting the eye drops for baseline measurements to assess their eligibility. On the first day of eye drop treatment, participants will be asked to remain at the clinic for approximately 3 hours to monitor for any acute side-effects. Subsequently, participants will be able to take their eye drops home where they will administer them once-daily (morning) for a period of four weeks. During the treatment period, participants will be asked to visit the University of Canberra Eye Clinic for weekly routine measures of vision and eye health. Participants will also be asked to visit the Eye Clinic four months after finishing the drops for follow-up measures.

WHAT ASPECTS OF THE TRIAL ARE EXPERIMENTAL?

The use of levodopa/carbidopa in a tablet form (at doses much higher than those that will be used in this study) is approved in Australia to treat neurological disorders. However, it is not currently approved as an eye drop, and is therefore currently classified as an experimental treatment. Therefore, this safety trial will test whether any ocular irritation or changes in normal vision occur when this medicine is given as an eye drop.
IS THIS TRIAL SAFE?

Clinical trials conducted in Australia are subject to a number of stringent regulatory controls to ensure the safety of all participants. In this trial, we will be investigating a compound (levodopa) that is classified as a low-risk medicine. As levodopa has been used for over five decades in humans to treat neurological disorders, considerable pre-clinical and human safety data exists. This safety trial will test whether any ocular irritation or changes in normal vision occur when this medicine is given as an eye drop. Such a trial is a formal requirement before any medicine can be used to treat a new disease for which it was not previously investigated for. No ocular irritation or changes in normal vision have been observed in pre-clinical testing for this eye drop solution. For a list of potential side effects associated with levodopa at doses well above those that will be used in this trial, please refer to the Participant Information Form provided.

WHAT ARE THE BENEFITS TO THOSE WHO PARTICIPATE IN THIS TRIAL?

As this is a safety and tolerability trial, there is no anticipated clinical benefit for participating in this trial. However, non-clinical benefits to participants include:

- Obtain a free and comprehensive analysis of your vision and eye health;
- Be part of advancing a treatment for the leading cause of visual impairment worldwide;
- Help improve the health of your local community, as well as those interstate and abroad;
- Help expand the impact of medical research in the ACT, and as such, improve our region’s ability to undertake critical clinical trials that will advance human health;
- There are no out-of-pocket costs associated with the trial;
- Snacks and refreshments will be provided at each clinical visit.

WHAT COMPENSATION OR TREATMENT IS AVAILABLE IN THE EVENT OF A TRIAL RELATED INJURY?

In the unlikely event that an adverse reaction is seen, the clinical team will immediately refer the participant for an independent assessment by an Ophthalmologist at The Canberra Hospital for evaluation and management. The participant will bear no cost, and all assessments will be organised by the clinical team. In the event of a trial related injury, participants will be covered under the Sponsor’s trial insurance (CAN21CT).

WHAT EXPENSES WILL PARTICIPANTS INCUR?

There will be no out-of-pocket costs associated with this trial.
IS PARTICIPATION VOLUNTARY?

Participation in the research is entirely voluntary, and you may, without any penalty, decline to take part. You may also withdraw from this study without providing an explanation, at any time, up until collection of the final measures. If potential participants tick any of the exclusion criteria in the pre-screening questionnaire, or are found to not be eligible during baseline measurement, they will be withdrawn from the study.

WHO WILL SEE THE TRIAL DATA AND PARTICIPANT INFORMATION?

Only the trial team, auditors, research ethics committee, and regulatory authorities will have access to de-identified raw trial data and information provided by participants. Privacy and confidentiality will be assured at all times. The research outcomes may be presented at conferences, written up for publication, or used within applications for additional clinical trials. Presented data will be de-identified, ensuring that the privacy and confidentiality of individuals will be protected.

WHAT HAPPENS IF NEW INFORMATION REGARDING THIS TREATMENT EMERGES?

If new information about the treatment becomes available during the trial period, the trial team will inform participants and discuss whether they want to continue treatment. If participants decide to continue in the trial, they will be asked to sign an updated consent form.

HOW DO PARTICIPANTS CONTACT THE TRIAL TEAM?

Queries or concerns regarding the clinical trial outlined in this document can be directed to the research team. Their contact details are found on the title page of this document. You can also contact the University of Canberra’s Research Ethics & Integrity Unit. You can either contact Dr Anesh Nair via phone (02 6201 5220) or email (humanethicscommittee@canberra.edu.au).

HOW MANY PARTICIPANTS ARE INVOLVED IN THIS TRIAL?

Thirty (30) participants will be enrolled in this trial.
Consent form

Project Title: Safety and tolerability trial of an ophthalmic treatment for short-sightedness

Consent Statement

1. I have read [or had read to me] and understand the information provided within this document which explains what this research project is about. I have had a chance to ask questions about the project, and I am comfortable with the answers that I have been given. I know that I can ask more questions at any stage.

2. I am not aware of any condition that would prevent my participation, and I agree to participate in this project.

3. I understand the purposes, procedures and risks of this project.

4. I voluntarily agree to my participation in this study and I understand that I can withdraw from the project at any time up until collection of the final measurements.

5. I understand that if I withdraw from this project, it won’t change my relationship with the trial team.

6. I am aware of, and agree to, my responsibilities in participating in this trial.

7. I understand that I will be given a signed copy of this document.

8. I understand that the results of this research may be published in a public or other forum. I know my name will NOT be mentioned in any published research outputs that come out of this research, and that people won’t be able to identify information that I provide.

9. I understand that my de-identified data may be shared with a third party for purposes such as publication, presentation of data, submission to regulatory boards, as well as applications for funding or further clinical trials. All presentation of such data to third parties will be de-identified.

10. I know that if I am worried about the research, I can contact Dr Regan Ashby at safety.trial@canberra.edu.au or Prof Nicola Anstice at nicola.anstice@flinders.edu.au. If I have concerns, I know that I can also contact the UC Human Ethics Committee, at HumanEthicsCommittee@canberra.edu.au.

I have read and agree to the Participant Information Form and Participant Consent Form.

Name……………………………………………………………………….……………………........…

Signature……………………………………………………………………………….

Date …………………………………

A summary of the research report can be forwarded to you when published. If you would like to receive a copy of the report, please include your email address below.

Email……………………………………………………………………………………………………