Clinical Trial Protocol

Investigational Medical Product

Effect and time course of topical dual-acting agents (antihistamine/mast cell stabiliser) and corticosteroids on ocular dendritic cell density, morphology, and topographical distribution in allergic conjunctivitis participants

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UNSW Coordinating Principal Investigator

Scientia Professor Fiona Stapleton

Contents

1. General Information

Protocol Title				
Effect and time course of topical dual-acting agents (antihistamine/mast cell stabiliser) and corticosteroids on ocular dendritic cell density, morphology, and topographical distribution in allergic conjunctivitis participants				
Protocol identifying number	**HC230343**			
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Human Research Ethics Committee	
Name	**HREC Committee C**
Status of ethical review	☐ **Approved** ☒ **In progress** ☐ **To be submitted**
Trial Sites	**UNSW Sydney**
Funding for the Clinical Trial	
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Amount of Funding	**NA**
Regulatory Requirements	
Therapeutic Goods Administration Clinical Trial Notification	☐ **Yes** ☐ **No**
Insurance for Clinical Trial	
Insurer	**UNSW**
Type of Insurance	
Confirmation of Insurance	☐**Attached** ☒ **In progress** ☐ **To be submitted**

2. Safety and Monitoring Contacts

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Independent Safety Monitoring Board or Data Safety Monitoring Board Members	
All interventions that will be used in this study are approved by the Therapeutic Goods Administration (TGA). Adverse events will be monitored and reported to ethics annually, except for serious adverse events, which will be reported as outlined in section 16 (within 48 hours).	
Trial Management Group	
• **Prof. Fiona Stapleton** • **Prof. Isabelle Jalbert** • **A/Prof. Blanka Golebiowski** • **Ali Alghamdi (PhD candidate)**	

3. Delegation of Clinical Trial Duties

Responsibilities for the conduct and oversight of the trial are delegated to you as the Coordinating Principal Investigator. You may delegate trial related responsibilities to the listed Principal Investigator(s) and any trial-related personnel. All trial-related duties delegated by the Coordinating Principal Investigator or Principal Investigator(s) and trial-related personnel must only be delegated to those qualified by experience and training. Delegated responsibilities must be retained in the UNSW Clinical Trial Delegation Log. In addition, the UNSW Sponsor's Delegate is to be notified of the following:

- Protocol deviation reports are outlined in the UNSW Research Misconduct Procedure.
- Any serious breach of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval that is likely to affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial.
- Significant safety issues that are likely to (or have the potential to) affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial.
- Urgent safety measures are implemented to remove or prevent a significant safety issue.
- Safety reports relating to the clinical trial's continuation, suspension, or discontinuation for safety reasons.
- Non-compliance with the protocol, SOPs, GCP, and applicable regulatory requirement(s) significantly affects or has the potential to affect human subject protection or reliability of trial results significantly.
- Participant complaints or concerns were received concerning the conduct of the research.
- Significant modifications to the clinical trial that is likely to affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial.
- Addition of participating trial sites, contractual arrangements at participating sites or modifications to legal agreements.
- The intention is to conduct the trial in other countries.

4. Trial Objectives and Purpose

This project aims to characterise the effect and time course of topical anti-allergy treatments on ocular surface dendritic cell density, morphology, and topographical distribution, and the relationships with changes in signs and symptoms of allergic conjunctivitis.

The research question that this study seeks to address is:
Do different therapeutic topical eyedrops (e.g., combination antihistamines and mast cell stabilisers versus corticosteroids) have different effects and time course on ocular surface dendritic cell density, morphology, and topographical distribution in allergic conjunctivitis patients?

The primary endpoint of the trial is the change in dendritic cell density (measured by counting their average number in a given area manually) using in-vivo confocal microscopy.

The secondary endpoints are the change in dendritic cell morphology (determined by measuring cell body size and presence of dendrites manually), using in-vivo confocal microscopy, and the change in eye allergy symptoms (including itchy eyes or watery eyes or burning feeling or feeling like there is dirt or grit in your eyes) and the change in eye allergy signs (including redness or conjunctival chemosis or conjunctival papillae or conjunctival follicles) and the possible relationship between ocular immune system and eye allergy clinical symptoms and signs.

5. Background Information

Allergic conjunctivitis is a group of diseases, that is usually bilateral and caused by the ocular response to various environmental and chemical air pollution allergens. The prevalence of allergic diseases has increased globally in the past few decades, and almost 1 in 5 Australians (19.6% of the total population) report some form of allergy [1-4]. The prevalence of ocular allergy is increasing worldwide, affecting individuals' quality of life, and causing a significant socioeconomic burden [5-8]. In a recent epidemiological survey of allergy prevalence in the US, 15 - 40% of the population reported having at least one ocular allergy symptom and were classified to have allergic conjunctivitis [9]. Allergic conjunctivitis can be managed using a range of options beginning with allergen avoidance and progressing to more complex treatments, including topical pharmacological agents such as decongestants, antihistamines, mast cell stabilisers, corticosteroids, non-steroidal anti-inflammatory drugs, and immunosuppressive agents [10-17].

Ocular dendritic cell play a substantial role in initiating the immune response in the setting of ocular allergies by capturing and processing antigens in peripheral tissue and migrating from the affected tissue to the lymph nodes via lymphatic vessels [18]. Once inflammation occurs, the phenotype of dendritic cell undergoes rapid change, antigen-capturing capability declines, and T-cell stimulation function increases [19]. However, the changes in ocular surface dendritic cell density and morphology were not associated with changes in ocular allergy symptoms or signs in the milder and severe forms of ocular allergy [20-21].

In a recently published article, dendritic cell density was higher in participants with allergic conjunctivitis at the corneal centre, corneal periphery, limbus, and conjunctiva but not at the inferior whorl, compared to controls [21]. Dendritic cell density was highest at the limbus followed by the corneal periphery and the lowest density was at the conjunctiva, and there was no difference between the corneal centre and the inferior whorl [21]. Dendritic cell morphology assessment was based on cell body size (small, medium, large), and the presence of any dendrites, the presence of long dendrites, and the presence of thick dendrites [21]. At corneal centre, dendritic cell had a larger cell body size, and there was a higher percentage of dendritic

cell with dendrites and with long dendrites in the allergic conjunctivitis group [21]. Cell body size, the presence of long dendrites and the presence of thick dendrites were not significantly different between groups at other locations [21]. When allergic participants were symptom free, corneal dendritic cell body size was smaller and there were fewer dendritic cell with long dendrites [22]. At the bulbar conjunctiva, dendritic cell density was reduced during the symptom-free phase but did not change in morphology [22].

The effect of the treatment of ocular surface disease on dendritic cell parameters has rarely been investigated [20-25]. Only two studies investigated these changes in allergic disease, specifically in vernal keratoconjunctivitis [24, 25]. Both studies reported a significant decrease in dendritic cell density, alterations in morphology, and in the presence of dendrites after starting the treatment. Liu et al. examined the dendritic cell density, distribution, and morphology of 35 vernal keratoconjunctivitis patients at the corneal limbus, peripheral cornea, and bulbar conjunctiva and found a significant decrease in dendritic cell density at the bulbar conjunctiva (after one month of treatment) and at the limbus and peripheral cornea (after 3 and 6 months of treatment) in patients treated with fluorometholone 0.1% (a corticosteroid eyedrop) or cyclosporine 0.5% (an immunosuppressant eyedrop) compared to baseline measurements [24]. At the end of the Liu study following treatment, dendritic cell appeared less reflective and had a smaller cell body size and dendrites or no dendrites [24]. Wan et al. found a significant decrease in all dendritic cell characteristics at the palpebral conjunctiva after two weeks of treatment using topical tacrolimus 0.1% (an immunosuppressant eyedrop) on 17 patients with tarsal vernal keratoconjunctivitis compared to baseline measurements [25]. After eight weeks of treatment, dendritic cell appeared as bright large cell without dendrites [25].

Overall, there is a paucity of evidence on the time course and effect of different treatments of allergic conjunctivitis on dendritic cell density and morphology, particularly for the more common and often milder forms of the disease such as allergic conjunctivitis. In addition, previous studies have not investigated or compared anti-allergy treatments. Moreover, the relationships between the time course of changes in dendritic cell characteristics and that of ocular symptoms and signs following anti-allergy treatment have not been explored.

This research is essential because it will help to fill the gaps in the current knowledge by exploring the time course effect of commonly used commercially available topical therapies (a combination antihistamine and mast cell stabiliser and a corticosteroid eyedrop) on dendritic cell density and morphology in allergic conjunctivitis. Dendritic cell density, morphology, and topographical distribution may serve as biomarkers of ocular allergy. Understanding the effect of different topical treatments on ocular dendritic cell will enhance our knowledge of the optimal treatment paradigms for allergic conjunctivitis and provide a potential future avenue for personalising the treatment of ocular allergies.

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2. Cook, M., et al., *The economic impact of allergic disease in Australia: not to be sneezed at*. 2007, Australasian Society of Clinical Immunology and Allergy (ASCIA). p. 41.
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Statement of Compliance

The clinical trial will be conducted in compliance with the following guidelines and documentation:

- ICH Guidelines for Good Clinical Practice (GCP)
- National Statement on Ethical Conduct in Human Research (National Statement)
- As approved by the Human Research Ethics Committee (HREC), the clinical trial protocol monitors the trial's conduct.
- The UNSW Sponsors Delegate sets out the responsibilities.
  The onsite or remote monitoring standard operating procedures as put in place by the clinical trial sponsor.

6. Conflicts and Interests

There are no conflicts of interest to disclose.

7. Trial Design

- This study is a single centre, double-blinded, randomised, placebo-controlled clinical trial.

The trial includes a 2-week double-blinded treatment period and a 2-week post-treatment follow-up with a total of 7 visits (including the assessment of eligibility visit) (Fig. 1). 90 participants will be randomly assigned (based on a pre-determined computer-generated list) to one of 3 groups (1:1:1) to receive unpreserved ketotifen 0.025% eyedrops as a dual-acting agent biweekly, unpreserved prednisone sodium phosphate 0.5% eyedrops biweekly or unpreserved 0.175% hydroxypropyl guar, 0.4% Polyethylene glycol 400, 0.3% propylene glycol, 0.15% sodium hyaluronate ocular lubricant eyedrops biweekly (Systane Hydration Unit Dose 0.7ml) as control.

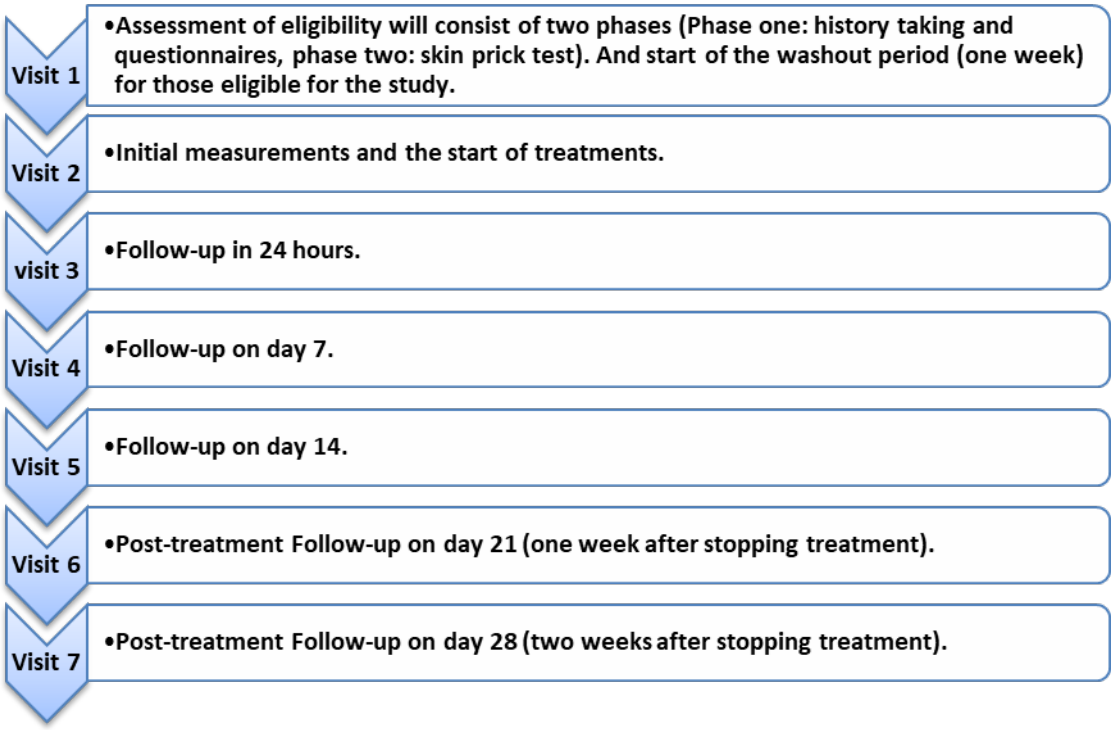

Figure 1 Clinical trial visits.

Eligible participants are those who have a history of experiencing symptoms of eye allergy and have prior diagnosis of hay fever, allergic rhinitis, rhinoconjunctivitis, or eye allergies (Seasonal and perennial allergic conjunctivitis). Participants should have current symptoms and signs of active ocular allergy at the time of study visit. Participants will be over 18 years old. This is a single-centre study and will be conducted at the School of Optometry and Vision Science at UNSW Sydney.

To limit bias, the trial is double-blind, keeping all participants, investigators, and all staff involved in the conduct of the trial blinded to the treatment administered. Eligible participants for this trial will be randomly assigned (based on a pre-determined computer-generated list) to 3 groups to receive either of the study interventions. All interventions are supplied as unit dose unpreserved formulations commercially available in Australia and registered on the ARTG. Intervention categories will be pre-packed in sealed envelopes and randomly labelled (intervention A, intervention B, and intervention C). Each envelope will have a sufficient amount of dosage for the treatment period.

- A schematic diagram of trial design is shown in Figure 2.

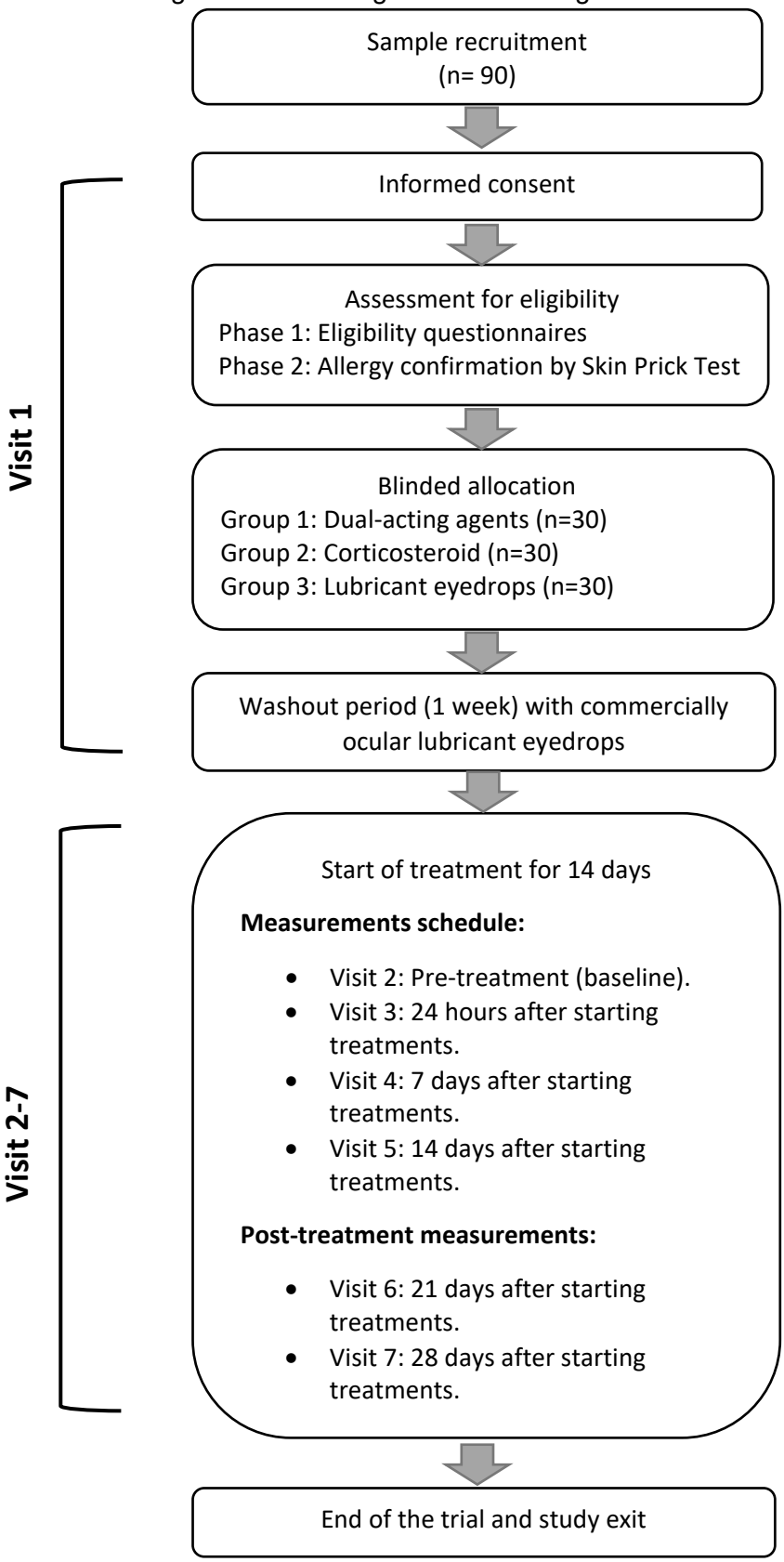

Figure 2 Trial flow diagram

8. Sample Size

The plan is to enroll 90 subjects to complete the trial.

The overall sample is comprised of the following samples from each of the participant groups:

1. **Participant Group 1** [Topical antihistamine + mast cell stabiliser]: [30 participants]
2. **Participant Group 2** [Topical corticosteroid]: [30 participants]
3. **Participant Group 3** [Topical ocular lubricant]: [30 participants]

Sample size calculation was undertaken using GPower 3.1. The nominated sample is based on based on the expected effect size at the central cornea dendritic cell density (0.512), from a previous study [1], alpha (0.05), and power of (0.8). The sample size will be 25 participants in each arm. The sample size will be adjusted by 20% to compensate for expected withdrawals. Therefore, the total sample size would be 90 participants for all arms, 30 participants in each arm, to ensure 75 participants complete the study after accounting for 20% drop out rate. This sample size is sufficient to meet the research aims and will address all the research questions. By this sample size, the power calculation reveals that this sample size will allow for statistically significant results.

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9. Selection and Withdrawal of Subjects

9.1 Inclusion Criteria

1. Be at least 18 years of age or older.
2. Positive result in the skin prick test.
3. All participants must have current active allergic conjunctivitis symptoms (including itchy eyes or watery eyes or burning feeling or feeling like there is dirt or grit in your eyes) or signs (including redness or conjunctival chemosis or conjunctival papillae or conjunctival follicles), with or without a prior diagnosis of ocular allergy or hay fever.
4. Able to read and comprehend English and give informed consent as demonstrated by signing a record of informed consent.

9.2 Exclusion Criteria

1. Severe allergic conjunctivitis (reflective from the total symptoms scores of the Mini-RQLQ and OSDI questionnaires) including vernal keratoconjunctivitis and atopic keratoconjunctivitis.
2. Negative result in the skin prick test.
3. Severe asthma.
4. Severe eczema.
5. Past anaphylactic episode.
6. Previous allergic reaction to any component of topical eyedrops used in this study including benzalkonium chloride preservative.
7. Pregnant or breastfeeding/childbirth within three months from the date of recruitment.
8. Regular contact lens wear (wearing contact lenses for at least two or more full days in a week).
9. All other ocular surface diseases except allergic conjunctivitis.
10. Ocular diseases that involve the cornea.
11. Active intraocular inflammation.
12. History of corneal refractive surgery.
13. Systematic conditions affecting the ocular surface include diabetes, thyroid disorder, rheumatoid arthritis and Sjögren syndrome.

9.3 Recruitment Strategy

Participants will be recruited via printed advertisements, posters and flyers distributed throughout UNSW and the surrounding general communities of Kingsford and Randwick, and those interested in participating will contact the research team via telephone or email provided in the printed adverts.

A digital format of this advertisement will be posted as a link on the UNSW School of Optometry and Vision Science website, circulated via screen advertising in the school and clinic, and emailed to the school staff and students. Email invitations will be sent individually to previous participants who have expressed interest in participating in future studies. Emailed recipients will not be able to see the contact details of others on the distribution list.

On all recruitment posts, the key inclusion criteria of age (at least be 18 years old) and current active allergic conjunctivitis symptoms and signs will be emphasised. It will explicitly acknowledge that if participants are interested in taking part in the research, they will need to initiate contact with the research investigators via email. Those interested in the study will be provided with a copy of the Participant Information Statement and Consent form by email.

9.4 Screening

The first email exchange between participants and the research investigators will entail a copy of the Participant Information Statement and Consent Form, which demonstrates the screening procedure, and key inclusion and exclusion criteria outlined in section 9. Once they pass the screening procedure, a date will be set for the participant visit. The participants will read and sign the informed consent form prior to data collection. Ineligible subjects will be notified and excluded from the study immediately. For participants who withdraw their study consent, no additional data will be collected. However, measurements and confocal microscopy collected before the withdrawal will be retained and analysed.

Screening process:

After participants have contacted the investigators regarding their interest, an email will be sent to the participants as part of a screening procedure. This will include questions regarding the key inclusion and exclusion criteria.

The investigators will conduct two eligibility phases (phase 1: eligibility questionnaires and phase 2: eligibility confirmation by the Skin Prick Test results) on the screening day. Phase one takes place at the School of Optometry and Vision Science, UNSW. The investigator will ask questions about ocular allergy or hay fever symptoms including itchiness and watery eyes, sneezing, or running nose, and interested participants will be asked to answer additional questionnaires to assess their eligibility for the study. They will take part in a preliminary examination which includes visual acuity assessment and ocular health check in order to exclude undiagnosed eye diseases.

In the second phase, a Skin Prick Test which takes approximately 15 minutes to complete will be conducted on the same visit day, under medical supervision at the UNSW Health Service After determining the eligibility of the participants and signing of the consent form. Included participants will be asked to complete a washout period of 1 week duration for which they will be given commercially available ocular lubricant eyedrops (Blink Intensive Tears eyedrops, ARTG ID:158805) and will be asked to install two drops daily in both eyes for 1 week. Eligible participants with active allergic conjunctivitis based on current active allergic conjunctivitis symptoms (including itchiness or watery eyes or burning feeling or feeling like there is dirt or grit

in your eyes) or signs (including redness or swollen eyelids), with or without a prior diagnosis of ocular allergy or hay fever will be randomly assigned (based on a computer-generated list) to 3 groups to receive either topical antihistamine and mast cell stabiliser eyedrops (dual-acting agent), or corticosteroid eyedrops in the treatment group, or lubricant eyedrops as the control group. Intervention categories will be pre-packed in sealed envelopes and randomly labelled (intervention A, intervention B, and intervention C). Each envelope will have a sufficient amount of dosage for the treatment period.

All the clinical tests will be conducted at the School of Optometry and Vision Science, UNSW. The skin prick test will be conducted at the University Health Service, UNSW, located at the Kensington campus with access to medical care in an unlikely event of an emergency.

9.5 Consent

A consent form and participation information sheet will be provided to the participants after they have initiated contact with the research investigators regarding their interest in participation. This information will detail the entire research including the purpose, research participating hours, risks involved, reimbursement, participant confidentiality and contact details of the investigator. There will be no coercion as the potential participants will be obtaining information of the study from posters on the bulletin board or from pamphlets given to them after their consultation in the UNSW clinic. They will also be reminded that their participation is completely voluntary, and they can withdraw at any time.

9.6 Withdrawal of Consent or Participant

- The participants have the right to withdraw from the trial at any time for any reason, without the need to justify their decision. However, the Investigator should record the reason for the patient's withdrawal, if possible. The investigator also has the right to withdraw participants.
- Participants will be withdrawn in the following circumstances:
- A participant's desire to withdraw for any reason.
- Loss to follow-up (every effort must be made to contact the participant; a certified letter must be sent or phone calls)
- An adverse event which, in the opinion of the Investigator and/or Sponsor, necessitates withdrawal.
- A participant's substantial non-compliance (e.g., visits non-compliance) after the start of the trial.
- The investigator's opinion that continuing the participant in the trial is not appropriate. The investigator may withdraw a participant at any time if it is considered to be in the participant's best interest.
- Participants suffering a worsening in disease are to be withdrawn. Worsening will be defined as an increase from the last visit in symptoms and signs score. Such worsening should be evaluated by the investigator and confirmed by slit lamp examination (no improvement or worse symptoms and signs) prior to deciding whether or not to withdraw the patient.

In case the participant has withdrawn consent, no new data can be entered into the record form. Any withdrawal must be fully documented in the report form and registered in as discontinued. If the reason for discontinuation is an adverse event, the specific event will be recorded in the report form. Withdrawn participants will not be replaced.

In case the investigator becomes aware of any serious adverse events (SAEs) or related non-serious adverse events in a withdrawn participant after trial completion these will be reported to HREC.

HREC may temporarily or permanently discontinue the trial at an investigational site at any time for safety, ethical, compliance or other reasons. If this is necessary, HREC will endeavour to provide advance notification to the site. If the site or trial is suspended or discontinued, the Investigator/Investigative Staff will be responsible for promptly informing HREC that this has happened.

10. Treatment of Subjects

Participants will undergo the following procedures:

- **Skin Prick Testing:**
  This test is for the confirmation of allergy eligibility as set by the inclusion criteria and will be conducted at phase two of the eligibility examination as described in section 10.4. A standard Skin Prick Test for common Sydney-based region indoor and outdoor aeroallergens will be conducted on each participant using extracts of ten chosen allergens (Stallergenes, Antony, France). Allergens will include four grass pollens (Rye: Lolium perenne, Bermuda: Cynodon dactylon, Paspalum: Paspalum notatum and Johnson: Sorghum halepense), two tree pollen (Cypress: Cupressus arizonica and Olive: Olea europaea), two dust mites (DP: Dermatophagoides pteronyssinus and Farinae: Dermatophagoides farinae), plant pollen (Plantain: Plantago lanceolata), the mold Alternaria and cat and dog dander.
  A drop of each allergen will be placed on the forearm, and a slight skin prick will be made using a lancet at the same spot to allow the allergen to be absorbed by the skin. Ten minutes later, the skin's allergic reaction will be determined by measuring the size of the hive formed on the skin.

- **History taking:**
  A review of demographics, ocular and medical history will be conducted verbally.

- **Questionnaires**
  Participants will be asked to complete questionnaires related to eye and nose allergy symptoms and participants' quality of life: Numerical Rating Scale (NRS) [1, 2], Mini Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ) [3], Ocular Surface Disease Index (OSDI) [4], Aston University Allergy Questionnaire (AUAQ) [5], the dry eye questionnaire for the detection of dry eye (Dry Eye Questionnaire: DEQ-5) [6], and the Eye Allergy Patient Impact Questionnaire (EAPIQ) [7]. Changes in symptoms and signs will be recorded, reported and analysed from both eyes as appropriate.

- **Visual acuity assessment**
  Measurement of the standard of vision achieved with the participants' usual spectacle correction in place (if any), will be measured using standard letter charts. Measurements will be taken separately for each eye. Pinhole acuity will be attempted for those without 6/6 vision.

- **The Perkins Tonometer**
  The Perkins tonometer is a handheld applanation model used to measure intraocular pressure. The principle of applanation tonometry is based on the force required to flatten a certain area of the spherical surface of the cornea is the same as the pressure inside the eye. The Perkins tonometer is a very popular handheld applanation tonometer used in humans.

- **The Oculus Keratograph 5M (K5)**
  This is an advanced corneal topographer with a built-in real keratometer and a colour camera optimized for external imaging. In our study the tear film break-up time will be measured automatically and non-invasively.

- **Slit lamp biomicroscopy**
  The ocular surface and anterior segment will be examined using a slit lamp biomicroscope and ocular surface signs, including conjunctival and limbal redness (graded using the Cornea and Contact Lens Research Unit (CCLRU) grading scale), conjunctival chemosis, papillae and follicles (graded using the Japanese grading scale for allergic conjunctivitis [8].

- **Ocular staining**
  A wetted fluorescein strip (harmless yellow dye) and a wetted lissamine green strip (harmless green dye) will be then gently touched to the fornix of the lower lid. Participants will be asked to blink continuously to enable the smooth spreading of the stain over the eye, allowing for the evaluation of any surface defects. Ocular surface (corneal and conjunctival) staining will be assessed using the Oxford grading scale [9]. These dyes are routinely used in optometry practices worldwide and are safe to use.

- **Confocal microscopy**
  A confocal microscope will be used to visualise the corneal sub-basal corneal nerves and dendritic cell in vivo. A probe that emits harmless laser light will come in contact with the transparent front part of the eye for approximately 5 minutes, and microscopic images of the cornea will be captured. Images will be captured from the right eye only. To avoid any discomfort to the patient or causing abrasions on the transparent surface of the eye a topical anaesthetic will be installed in the tested eye and a soft lubricating gel will be applied over the microscope probe.

All the above-mentioned clinical procedures (except the Skin Prick Test) will be repeated for the eligible participants at the follow-up visits.

Reference list

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11. Investigational Medical Product and Trial Intervention

The interventions in this trial are unpreserved unit dose ketotifen 0.025% eyedrops as a dual-acting agent and unpreserved prednisolone sodium phosphate 0.5% eyedrops.

Zaditen (ketotifen) 0.025% (ARTG ID 113770)

- Active substance: ketotifen.
- Manufactured by: Novartis Pharmaceuticals Australia Pty Limited.
- Application form: Topical eyedrop.
- Formulation: Glycerol, Sodium hydroxide, water for Injections.
- Packaging /units per package: Vials 0.4ml (250 µg in 1mL).
- Storage (incl. specific storage guidance): ketotifen is stored below 25°C.
- Market authorisation in Australia: Yes.

Prednisolone sodium phosphate 0.5% (ARTG ID 32233)

- Active substance: 0.5% w/v of Prednisolone Sodium Phosphate.
- Manufactured by: Bausch & Lomb (Australia) Pty Ltd.
- Application form: Topical eyedrop.
- Formulation: Prednisolone sodium phosphate 0.5% w/v as well as disodium edetate, monobasic sodium phosphate, sodium chloride, sodium hydroxide and purified water.
- Packaging /units per package: Each unit contains approximately 0.5mL solution in a container that has a twist and pull cap. Each unit should be discarded after a single use. The solution has a neutral pH.
- Storage (incl. specific storage guidance): prednisolone phosphate is stored between 2 - 8°C.
- Market authorisation in Australia: Yes.

The control intervention is an unpreserved lubricant eyedrop (Systane Hydration Unit Dose 0.7 ml).

Systane Hydration Unit Dose 0.7 ml (ARTG ID 308516)

- Active substance: Polyethylene Glycol 400 0.4%, Propylene Glycol 0.3%.
- Manufactured by: Alcon Laboratories Australia Pty Ltd.
- Application form: Topical eyedrop.
- Formulation: Sodium hyaluronate, polyethylene glycol 400, propylene glycol, hydroxypropyl guar, sorbitol, aminomethyl propanol, boric acid, sodium borate, potassium chloride and sodium chloride.
- Packaging /units per package: Each unit contains 0.7 ml.
- Storage (incl. specific storage guidance): Systane Hydration is stored 5 - 25°C.
- Market authorisation in Australia: Yes.

The washout eyedrops is an unpreserved lubricant eyedrops (Blink Intensive Tears Protective Eye Drops - Unit Dose - Lubricant, eye)

Blink Intensive Tears Protective Eye Drops - Unit Dose - Lubricant, eye (ARTG ID 158805)

- Active substance: Polyethylene Glycol 400 0.25%
- Manufactured by: Johnson & Johnson Surgical Vision Inc.
- Application form: Topical eyedrop.

- Formulation: 0.25% polyethylene glycol 400 (PEG 400), purified water, boric acid, sodium hyaluronate, potassium chloride, sodium chloride, sodium borate, calcium chloride, magnesium chloride.
- Packaging /units per package: Each unit contains 0.4 ml.
- Storage (incl. specific storage guidance): Systane Hydration is stored less than 25°C.
- Market authorisation in Australia: Yes.

Ocular lubricant eyedrops (Blink Intensive Tears eyedrops) will be provided to all participants during the washout period and will be asked to install two drops daily in both eyes for 1 week. All medications used in this trial are unpreserved to minimise the possibility of these preservatives impacting the trial results. Only trained optometrists are to be delegated these responsibilities. All medications given in this trial will be prescribed by registered optometrists.

12. Storage, dispensing and product accountability.

All medications and control eyedrops used in this trial will be stored securely at the School of Optometry and Vision Sciences (Rupert Myers building), with access limited to study investigators. All medications and control eyedrops will only be dispensed to participants who meet the eligibility criteria and are randomised to a treatment group in the trial. The Investigator (or his/her blinded designated personnel) will maintain a participants Medicine Dispensing Log detailing the medication numbers and dates of medication dispensed for each participant during the course of the trial. Only trained optometrists are to be delegated these responsibilities.

Participants will be instructed to discard used medications and control eyedrops in the appropriate way as per manufacturer guidelines. Unused medications and control eyedrops will be destroyed at the trial site in accordance with local requirements and when site operating procedures permits after the drug accountability has been finalised and signed-off by the Investigator.

13. Randomisation and Allocation

This study is a single centre, double-blinded, randomised, placebo-controlled clinical trial. Eligible participants will be randomly allocated to one of the three study groups in a 1:1:1 ratio based on a pre-determined computer-generated list to ensure every participant has an equal chance of being allocated to any treatment arm. All interventions that will be used in this trial will come in transparent ampules. Originally labelled intervention ampules will be masked by covering the drug information with opaque labels. Intervention ampules will be removed from the original packaging and pre-packed in sealed envelopes, and randomly labelled (intervention A, intervention B, and intervention C). Each envelope will have instructions of use and a sufficient amount of dosage for the treatment period. Each group will be randomly assigned to receive either topical antihistamine and mast cell stabiliser eyedrops (dual-acting agent) or corticosteroid eyedrops in the treatment group and lubricant eyedrops as the control group. The pre-packing of the eyedrops will be allocated to external personnel (not a member of the investigators' group). The external personnel will be responsible for maintaining the randomisation list. The randomisation process will be held at the School of Optometry and Vision Science. No specific experience or qualification is required by the personnel delegated these responsibilities.

An emergency decoding possibility, computer-based or other, will be available to the Investigator and to designated investigators. Breaking of the blind for individual patients in emergency situations is an Investigator responsibility. As far as the emergency permits, the need to break the blind will be communicated to HREC. The unblinding in emergency situations is only permitted in case of a suspected, unexpected serious adverse reaction (SUSAR) or other important adverse event, when the knowledge of the trial medications in question is required for

therapeutic decisions for the management of the participant. The Investigator who unblinds a treatment must record the reason and date for unblinding before the treatment code can be broken. The Investigator must record the event of unblinding in the participant's record, including the reason for unblinding, but not the treatment allocation if this can be avoided. In case of accidental unblinding, the same documentation as for emergency unblinding must be obtained.

If HREC needs to unblind a treatment, the reason and the date of opening should be recorded with signature, following standard operational procedures for unplanned unblinding of clinical trial participants. It should be recorded in the subject's source documents that the code is broken, why, when and by whom.

If it is necessary to unblind an individual participant's treatment for the purposes of expedited reporting to the authorities and/or ethics committee, only those individuals whose responsibility it is to report this information will know the identity of the medication. Every attempt will be made to ensure that all other trial and site staff will remain blinded throughout the course of the trial.

Information on whether the blind has been broken for any patients must be collected before the database is declared clean and analysed. No specific experience or qualification is required by the personnel delegated these responsibilities.

14. Treatments, Dosing, Dosage Schedules, and Route of Administration

After taking history, participants will be asked to complete questionnaires (eligibility phase 1), related to eye and nose allergy symptoms: Numerical Rating Scale (NRS), Mini Rhinoconjunctivitis Quality of Life Questionnaire (Mini-RQLQ), Ocular Surface Disease Index (OSDI), Aston University Allergy Questionnaire (AUAQ), the dry eye questionnaire for the detection of dry eye (Dry Eye Questionnaire: DEQ-5) and the Eye Allergy Patient Impact Questionnaire (EAPIQ). Changes in symptoms during the treatment will be recorded using a Numerical Rating Scale (NRS). Changes in symptoms and signs will be recorded, reported and analysed from both eyes as appropriate. Each questionnaire includes detailed instructions on how to complete them. To confirm participants' allergy status, a Skin Prick Test will be conducted (eligibility phase 2) where a drop of allergen will be placed on the forearm, and a slight skin prick will be made using a lancet at the same spot to allow the allergen to be absorbed by the skin. Ten minutes later, the skin's allergic reaction will be determined by measuring the size of the hive formed on the skin. Visual acuity, Tearscope and ocular surface health integrity with white light slit lamp biomicroscopy will follow. Ocular staining will be performed before and after each time taking confocal microscopy images.

Ocular surface dendritic cell images will be taken using the *in vivo* confocal microscopy (IVCM) at the baseline visits and at each follow-up visit. A topical anaesthetic eyedrops will be applied to the examined eye of the participants (right eye) and a soft lubricating gel will be applied over the microscope probe to avoid any discomfort. Participants will be directed to look at a single white fixation light with the contralateral eye to help maintain head posture and eye position. A gentle touch by the IVCM probe will be apply on the corneal surface (the transparent front part of the eye) to capture multiple images from different locations on the cornea.

After the baseline visit, participants will be randomly given either treatment or control eyedrops and instructed to put one drop in each eye, twice daily for two weeks. Participants will be asked to visit the clinic at different interval periods including 24 hours, 7 days and 14 days during the treatment period, and post-treatment at days 21 and 28, to repeat all the examinations except the Skin Prick Test (Table 1).

All study groups will undergo the same measurements and test procedures (Table 1). Participants using eye and/or general medication known to affect eye health or eye comfort before or during the study will be excluded. The personnel to whom the above listed responsibilities are delegated should be trained clinicians.

	Visits								
		One week Wash-out period	Treatment visits (14 days)				End of the treatment period	Post-treatment visits (14 days)	
Conducted procedure (Approximate time)	Visit 1 (2 hours)		Visit 2 (1 hour)	Visit 3 (1 hour)	Visit 4 (1 hour)	Visit 5 (1 hour)		Visit 6 (1 hour)	Visit 7 (1 hour)
Medical history	X								
Questionnaires and record forms	X		X	X	X	X		X	X
Skin prick test	X								
Visual acuity			X	X	X	X		X	X
Perkins Tonometer			X	X	X	X		X	X
The Oculus Keratograph 5M (K5)			X	X	X	X		X	X
Slit lamp examination			X	X	X	X		X	X
Ocular staining			X	X	X	X		X	X
Confocal microscopy			X	X	X	X		X	X

Table 1: Table of Procedures

15. Safety and Monitoring

15.1 Assessment of Safety Event Report Forms

Safety reports will be assessed based on the seriousness, causality, and expectedness of the event to the trial treatment(s), intervention(s), investigational medical product(s), investigational medical device(s). The following are known and expected adverse effects, harms, risks, or discomforts associated with trial procedures, treatments or interventions.

a) Known Adverse Effects

- minor side-effects of medications used in this study (e.g., corneal abrasions, eye irritation, eye pain, blurred vision and/or problems seeing clearly, photophobia),
- the discomforts related to optometric measurements (e.g., tearing, potential corneal abrasions)
- the discomfort related to the skin prick test (e.g., swelling of the examined area, feeling of dizziness, light-headedness)

b) Known Harms, Risks or Discomforts

- Ocular medication harms: including injury, punctate keratitis, severe corneal erosion, severe corneal abrasions, and cataract.

15.2 Adverse Events or Adverse Reactions

Adverse events (AE) are defined as any untoward medical occurrence in a patient or clinical trial participant administered the investigational medical product or intervention, which does not necessarily have a causal relationship with this treatment.

Adverse Reactions (AR) are defined as any untoward and unintended response to the trial intervention related to any dose administered.

AEs and ARs are assessed using the safety monitoring flow chart. Those classified as "not serious" are assessed by the qualified physician/medical expert specified in section 2 of the protocol. The Qualified Physician cannot delegate this responsibility to other research personnel.

Adverse event will be monitored and reported annually to HREC. In addition, all adverse event reports must be recorded in the UNSW Safety Monitoring Register Template.

15.3 Serious Adverse Events

Serious Adverse Events (SAEs) that result in or lead to one or more of the following and the event is **not related** to the investigational medical product, the trial intervention, or procedures:

- The death of a trial participant.
- A life-threatening illness or injury involving a trial participant.
- A participant's permanent impairment of body structure or body function.
- A trial participant is an in-patient or prolonged hospitalisation (not for a pre-existing condition or an elective surgery).
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or function of a trial participant.
- Fetal distress, fetal death, congenital abnormality or birth defect.

SAE reports are classified following the safety assessment flowchart and are assessed by Sponsors Independent Medical specified in section 2 of the protocol. The Sponsors Independent Medical cannot delegate this responsibility to other research personnel. SAE reports are reported to HREC within 48 hours. SAR reports must be recorded in the UNSW Safety Monitoring Register Template.

15.4 Serious Adverse Reactions

A Serious Adverse Reactions (SAR) is an SAE **related** to the investigational medical product, the trial intervention, or procedures. SAR reports are classified following the safety assessment flowchart and are assessed by Sponsors Independent Medical specified in section 2 of the protocol. The sponsors independent medical expert must determine whether the SAR was expected or unexpected. The Sponsors Independent Medical cannot delegate this responsibility to other research personnel.

a) Expected Serious Adverse Reaction

A serious adverse reaction by its nature, incidence, severity, or outcome is anticipated and identified in the current investigational medical product or intervention safety information, classified as a SAR report. SAR reports are reported to the Coordinating Principal Investigator 48 hours. In addition, serious Adverse Reaction reports must be recorded in the UNSW Safety Monitoring Register Template.

b) Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction by its nature, incidence, severity, or outcome is unanticipated and not identified in the investigational medical product, the trial intervention, or procedures for use safety information are classified as a SUSAR.

Fatal or life-threatening Australian SUSAR reports are reported to the Therapeutic Goods Administration, the Coordinating Principal Investigator, and the sponsor's delegate within seven calendar days after being made aware of the case follow up information reported within a further eight calendar days.

All other Australian SUSAR reports are to be reported to the Therapeutic Goods Administration, the Coordinating Principal Investigator, and the sponsor's delegate within 15 calendar days after being made aware of the case follow up information reported within a further eight calendar days. In addition, SUSAR reports must be recorded in the UNSW Safety Monitoring Register Template.

15.5 Significant Safety Issue (SSI)

A safety issue that could adversely affect participants' safety or materially impact the trial's continued ethical acceptability or conduct. The Therapeutic Goods Administration, Human Research Ethics Committee and Sponsor's Delegate must notify all significant safety issues within 15 calendar days of the sponsor instigating or being made aware of the issue**.** SSI reports must be recorded in the UNSW Safety Monitoring Register Template.

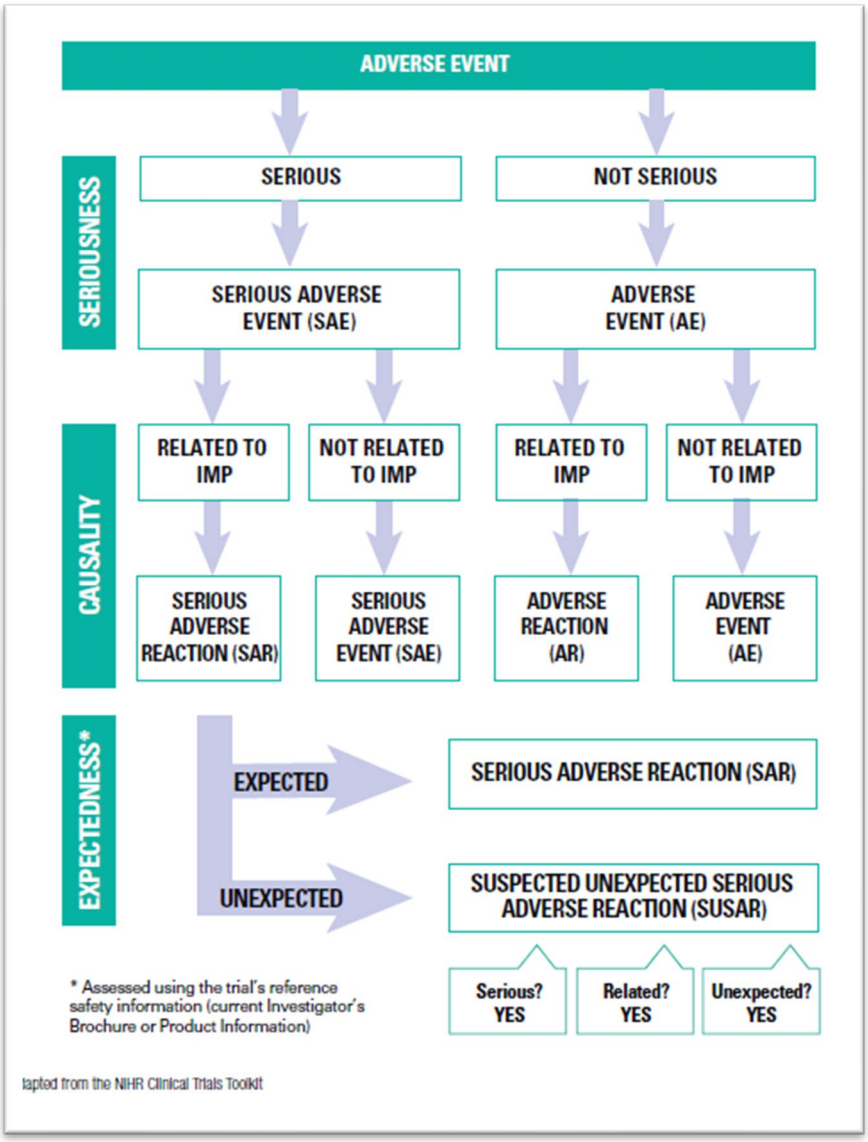
15.6 Urgent Safety Measure (USM)

A measure that is taken to eliminate an immediate hazard to a participant's health or safety. Significant safety issues requiring an urgent safety measure to be taken to eliminate an immediate hazard must be classified as a significant safety issue requiring an urgent safety measure. The Therapeutic Goods Administration, Human Research Ethics Committee and the Sponsor's Delegate must be notified of any significant safety issues that meet the definition of an urgent safety measure should be notified within 72 hours. Examples include:

- a serious adverse event that could be associated with the trial procedures and that requires modification of the conduct of the trial.
- A patient population hazard, such as lack of efficacy of intervention used to treat a life-threatening disease.

USM reports must be recorded in the UNSW Safety Monitoring Register Template.

15.7 Safety Assessment Flow Chart Investigational Medical Product Trials



15.8 Register of Clinical Trial Safety Monitoring Reports

A register of all event reports assessed and classified is to be retained by the Coordinating Principal Investigator and reported to the trial sponsor annually and the HREC if required.

15.9 Reporting of Clinical Trial Safety Monitoring Reports

Single case reports of Adverse Events Adverse Reactions, Serious Adverse Events (SAEs), and Serious Adverse Reactions (SARs) do not need to be reported to the UNSW Sponsor's Delegate or the HREC. However, all case reports must be recorded in a safety monitoring register and reported annually to the UNSW Sponsor's Delegate.

a) Emerging Safety Issues

The Trial Management Group, Trial Safety Committee is responsible for reviewing the safety information to identify any serious emerging safety concerns. If safety concerns are identified, this body will establish a plan to minimise the time participants may be placed at

excess risk of harm. Before implementing the plan, the Trial Management Group, Trial Safety Committee must seek the advice of the human research ethics committee.

b) Annual assessment of safety

The following information must be provided in a report annually:

- Documented evidence that the Trial Management Group, Trial Safety Committee, or the Data Safety Monitoring Board (e.g., meeting minutes) confirmed that regular safety reviews occurred.
- Analysis of the trial intervention(s) and its implications for participants considering all available safety data and relevant clinical or non-clinical studies results.
- Any reports of emerging safety issues and a description of any measures taken or proposed to minimise risks.
- A copy of the safety monitoring register.

16. Non-compliance, Protocol Deviation and Serious Breaches of Good Clinical Practice

16.1 Protocol Deviation

A protocol deviation is defined as any breach, divergence or departure from the requirements of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval that does not have a significant impact on the continued safety or rights of participants or the reliability and robustness of the data generated in the research or clinical trial. Protocol deviations are events that do not occur persistently or systematically and do not potentially result in participant harm. Examples of protocol deviations include but are not limited to:

- Deviations because of participant adherence to the protocol, including rescheduled study visits, participants refusal to complete scheduled research activities or failure to complete self-report questionnaires required by the study protocol.
- Blood samples obtained or clinical trial testing occurring at times close to, but not precisely at the time specified in the protocol.
- The completion of consent forms, safety monitoring reports, case report forms or data collection tools in a manner that is not consistent with the protocol instructions or failure to make reports within the required reporting timeframes.
- Administration of the clinical trial investigational medical product or device in a manner that is not consistent with the manufacturer's instructions for use.
- Use an unapproved version of the participant information statement or recruitment of participants using unapproved recruitment procedures.
- Inclusion of a participant that does not meet the inclusion criteria.
- An urgent safety measure must be taken to eliminate an immediate hazard to a participant's health or safety.

16.2 Serious Breach of Good Clinical Practice

A serious breach is defined as a breach of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval that is likely to affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial. Examples of serious breaches include but are not limited to:

- Persistent or systematic non-compliance with the instructions for completing consent forms, safety monitoring forms, case report forms or data collection tools result in continued missed or incomplete data collection.

- Failure to record or report adverse events, serious adverse events, suspected unexpected serious adverse reactions, significant safety issues where urgent safety measures were implemented.
- Failure to conduct clinical trial procedures following the clinical trial delegation log.
- Widespread and uncontrolled use of protocol waivers or deviations from eligibility criteria that (or has the potential to) harm trial subjects.
- Failure to report investigational medical product or device defects to the clinical trial sponsor or any relevant regulatory body.
- Failure to conduct research following the issued approvals, permits or licences by required laws, regulations, disciplinary standards, and UNSW policies relating to research's responsible or safe conduct.
- Concealing or facilitating breaches (or potential breaches) of the Research Code by others.
- Researching without the requisite approvals, permits or licences required by laws, regulations, disciplinary standards, and UNSW policies related to research's responsible or safe conduct.
- Failure to conduct research as approved by an ethics review body where that conduct leads to (or has the potential to) results in participant harm.
- Researching without ethics approval as required by the National Statement on Ethical Conduct in Human Research where that conduct leads to (or has the potential to) result in participant harms.
- Any breaches as outlined in the UNSW Research Misconduct Procedure or the Australian Code for responsible conduct of research that leads to (or has the potential to) result in participant harm.

16.3 Reporting Protocol Deviations

- Protocol deviations occurring at a site must be documented in site files and reported to the Coordinating Principal Investigator by the principal site investigator.
- The Coordinating Principal Investigator must review the protocol deviation and the clinical trial protocol to establish the corrective actions and preventative steps to prevent the deviation from reoccurring.
- The protocol deviation and corrective action plan must be reported to the UNSW Sponsor's Delegate by the Coordinating Principal Investigator or Coordinating Research Team.

16.4 Reporting of a Serious Breach

- A serious breach occurring at a participating site must be reported by the site Principal Investigator to the Coordinating Principal Investigator within a specified timeframe.
- The Coordinating Principal Investigator must review the serious breach, along with the clinical trial protocol, to develop a Corrective and Preventive Action (CAPA) that defines the steps to prevent the serious breach from reoccurring.
- The serious breach report and the CAPA must be provided to the approving HREC, and the UNSW sponsors delegate for review and approval.

16.5 Reporting of Serious Breaches by Third Parties

- A Suspected Breach is a report judged by the reporter as a possible serious breach but has yet to be formally confirmed as a serious breach by the sponsor.
- A Suspected Breach form must be completed when a third party (e.g., individual/institution) wishes to report a suspected breach of Good Clinical Practice or the protocol and should be reported directly to the reviewing HREC.
- Recording of Protocol Deviation and Serious Breach Reports
- A register of protocol deviation and serious breach reports must be recorded. In addition, written records and copies of documentation must be retained in the Investigator Site File.

- Copies of protocol deviation and serious breach reports must be recorded, written records and copies of documentation, referrals made to the HREC or establishing whether a breach of the Australian Code for Responsible conduct of research must be retained in the Master Site File.

17. Review of a Protocol Deviation and a Serious Breach

- The UNSW Sponsor's Delegate will review reports to establish whether the event meets the definition of a protocol deviation or serious breach, establish whether the proposed CAPA is appropriate and establish whether there is or will be an ongoing impact on the reliability and robustness of the data generated.
- The UNSW Sponsor's Delegate will seek advice from the approving HREC on the corrective and preventive actions.
- Protocol deviation or serious breach reports where a UNSW researcher, staff or student is responsible for the protocol deviation or the serious breach will be reviewed as per the UNSW Research Misconduct Procedure to establish whether a breach of the UNSW Research Code Conduct has occurred.
- Protocol deviation or serious breach reports where the UNSW Sponsor's Delegate determines that site personnel are responsible for a protocol deviation or the serious breach will be referred onto their responsible institution for review under their Research Misconduct procedures to establish whether a breach of the Australian Research Code for the Responsible Conduct of Research has occurred.

18. Statistics

- SPSS software (version 28.0; SPSS inc.) will be used. Differences in symptoms and signs between treatment groups and the control group will be assessed using the Independent Sample t-test or Mann-Whitney U test, as appropriate. For dendritic cell density, A linear mixed model with effect for individuals will be used to examine differences in (log) dendritic cell density between groups and between corneal and conjunctival locations. Pairwise comparisons between groups and locations will be obtained within the model. P-values for multiple comparisons between locations will be adjusted by Holm's step-down Bonferroni method.
- Mann-Whitney U test (for cell body size) and Fisher's Exact test (for the presence of dendrites) will be used to assess differences in dendritic cell morphology between groups. Friedman, and Wilcoxon Singed Ranked Test (for cell body size) and Cochran's Q Test (for the presence of dendrites) will be used to assess differences in dendritic cell morphology across locations and the p-values for pairwise comparison between locations were adjusted by Holm's step-down Bonferroni method.
- Associations between dendritic cell and ocular surface symptoms and signs will be assessed using a univariate Spearman's correlation coefficient (for dendritic cell density and cell body size) and Mann-Whitney U test (for the presence of dendrites).

19. Data Handling, Ownership and Access

19.1 Data Ownership

All research data collected during this trial is governed and handled following the Research Data Governance and Materials Handling policy. UNSW, rather than any individual or Organisational Unit, is the Custodian of data and materials and any information derived from the data. Original research data and primary materials generated in the research conducted at the University will be owned and retained by the University subject to any contractual, statutory, ethical, or funding body requirements.

19.2 Authorship

Authorship will comply with UNSW Authorship policy (https://research.unsw.edu.au/authorship-publication)

19.3 Recording and Reporting Data

Principal Investigators are responsible for maintaining adequate and accurate source documents and trial records that include all pertinent observations on each site's trial subjects. Source data must be attributable, legible, contemporaneous, original, accurate, and complete.

Trial subjects will be assigned a participant ID, and data will be reported using the case report form.

Data will be reported on the case report form, derived from source documents, should be consistent with the source documents, or the discrepancies must be explained. Any change or correction to a case report form should be dated, initialled, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections.

Data is collected at the following timepoints before, during and after the treatment and entered into the case report form in electronic format.

19.4 Confidentiality

Information collected in the trial must be handled following the Privacy and Personal Information Protection Act 1998 (NSW) requirements. Trial subjects have the right to access personal information held about them by the UNSW and can request correction and amendment. The UNSW requirements to ensure that personal information is protected is available in the UNSW Privacy Management Plan.

19.5 Direct Access to Source Data and Documents

Site principal investigator(s) and institution(s) will permit trial-related monitoring, audits, HREC review, and regulatory inspection(s), providing direct access to source data/documents. The sponsor will not have access to source data. However, site(s) and institutions will allow the sponsors to monitor or auditor access to source documentation for auditing purposes.

20. Trial Management Group, Data Safety Monitoring Board, Independent Safety Committee

The Monitor will contact and visit the Investigator periodically to ensure adherence to the Protocol, Good Clinical Practice (GCP), standard operating procedures and applicable regulatory requirements, maintenance of trial-related source records, completeness, accuracy.

The Investigator will permit the Monitor direct access to all source data, including medical records, and/or documents in order to facilitate data verification. The Investigator will co-operate with the Monitor to ensure that any discrepancies that may be identified as resolved. The Investigator is expected to be able to meet the Monitor during these visits. When the first patient is allocated to treatment at the trial site, a monitoring visit will take place shortly afterwards. For this trial, the frequency of the monitoring visits is intended to be approximately every 6 months.

The Investigator will ensure that the confidentiality of the patients' data will be preserved. In the case report from or any other documents submitted to the Sponsor, the patients will not be

identified by their names, but by an identification system, which consists of an assigned number in the trial. Documents that are not for submission to the Sponsor (e.g. the confidential patient identification code and the signed Informed Consent forms), will be maintained by the Investigator in strict confidence.

21. Monitoring Quality Control and Quality Assurance

The Coordinating Principal Investigator and Principal Investigator(s) 'responsibility are to monitor the clinical trial. In addition, it is the responsibility of the Coordinating Principal Investigator and Principal Investigator(s) to undertake or participate in site initiation and or protocol-specific training before recruitment and data collection commences. A monitoring report demonstrating regular compliance with the clinical trial protocol, its procedures and the HREC approval is provided to the UNSW Sponsor's Delegate annually.

Root, cause, analysis reports are to be completed by the Coordinating Principal Investigator for reports of non-compliance and serious breaches. In addition, a corrective and preventative action plan must be developed and actioned for any reports of non-compliance and serious breaches.

22. Clinical Trial Research Agreement

The Coordinating Principal investigators must ensure that agreements are executed at each of the following sites before site initiation, recruitment, and data collection commences.

Templates for clinical trial research agreements can be downloaded using the following link:

- https://www.medicinesaustralia.com.au/policy/clinical-trials/clinical-trial-research-agreements/

- All agreements are to be negotiated with Research Grants and Contracts once the clinical trial protocol has been developed, human ethics approval has been established, and, where applicable, the UNSW Clinical Trials Sponsor's Delegate has confirmed that UNSW will act as clinical trial sponsor.
- Signed CTRAs and other agreements must be included in the list of GCP essential documents. Recruitment and data collection for a clinical trial must not commence without an executed CTRA in place.

23. Research Governance Site Authorisation

Site authorisation is to be obtained, or if a research site is added, a site authorisation letter from the delegated authority of an institution responsible for any participating site is obtained. It must be stored as a GCP essential document before participants are recruited at a participating site.

24. Site Closure or Termination of Trial

Once all participants have concluded the study the data will be cleaned, and the associated documents will be locked for posterior data analysis. Any remaining paper records will be stored in a locked filling cabinet and only approved research personnel will have access.

25. Good Clinical Practice Requirements

Coordinating Principal Investigators, Principal Investigators and all site personnel or trial-related staff must have current Good Clinical Practice Training. Evidence of training confirmation is to be stored as a GCP essential document.

It is the responsibility of the Coordinating and Principal Investigators to familiarise themselves with the requirements of the Guideline for Good Clinical Practice (E6, R2)

26. Essential Documents for the Conduct of a Clinical Trial

All essential documents referred to in section 8.2 of the Guideline for Good Clinical Practice (E6, R2) are to be retained by all trial investigators.

27. Qualifications and Curriculum Vitae

Copies of CVs for all principal investigators will be stored as an essential document. In addition, the TransCelerate CV template can be used as a template.

28. Clinical Trial Delegation and Responsibilities Log

Protocol / Study Number:		**Sponsor Name:**	UNSW
Principal Investigator Name:		**Site Number:**	
Site Name (if applicable)			

***THIS FORM IS TO BE COMPLETED BY ALL PERSONNEL INVOLVED IN THE STUDY AFTER RECEIVING PROPER STUDY TRAINING AND BEFORE TAKING PART IN ANY STUDY ACTIVITIES**

Principal Investigator (PI)

By signing, I confirm/acknowledge that the tasks listed below will only be delegated to appropriately trained, skilled and qualified staff. I will remain responsible for the study's conduct and reported data, ensuring study oversight. All associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations and have not performed any study tasks before appropriate delegation and completion of appropriate training. Mechanisms are in place to ensure that site staff receives the appropriate information and training throughout the study and that a 2-way communication channel exists between staff and self. Any changes in staff or delegation in staff will be recorded promptly.

Name	Principal Investigator's Signature	Initials	Start (dd/mmm/yyyy)	End (dd/mmm/yyyy) (complete only if prior to end of study)

Site Staff

Name	Signature	Initials	Study Role	Key Study Task(s) (choose from list below)	Start (dd/mmm/yyyy)	End (dd/mmm/yyyy) (complete only if prior to end of study)	PI Initials & Date (dd/mmm/yyyy)
							_____ __/___/____
							_____ __/___/____
							_____ __/___/____
							_____ __/___/____
							_____ __/___/____
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							_____ __/___/____
							_____ __/___/____

Name	Signature	Initials	Study Role	Key Study Task(s) (choose from list below)	Start (dd/mmm/yyyy)	End (dd/mmm/yyyy) (complete only if prior to end of study)	PI Initials & Date (dd/mmm/yyyy)
							_____ __/___/____
							_____ __/___/____
							_____ __/___/____

Comments:

Electronic Signature Declaration for Principal Investigator and Site Staff

- As it applies to entering electronic data or signing records in sponsor-owned or sponsor-outsourced computer systems, my electronic signature is the legally binding equivalent of my handwritten signature.
- I will not share the password(s) assigned to me for this study with any other persons.

Principal Investigator's End of Study Declaration

I, at this moment, confirm that the above information is accurate and complete and that I authorised the delegation of study-related tasks to each individual as listed above.

Principal Investigator's Signature: _____ **Date:**

Task Key:

1. Obtain informed consent *
2. Subject selection/recruitment*
3. Confirm eligibility (review inclusion/exclusion criteria)*
4. Obtain medical history (source documents)
5. Perform physical exam*
6. Conduct study visit procedure as outlined in the protocol*
7. Make study-related medical decisions*
8. Assess AEs/SAEs*
9. Dispense study drug*
10. Perform drug accountability
11. Study drug storage and temperature monitoring
12. Sample collection
13. Sample processing and/or shipment
14. Evaluate study-related test results *
15. Use IWRS/IVRS
16. Make entries/corrections on (e)CRFs
17. Sign- off (e)CRFs*
18. Maintain essential documents
19. Perform study-related assessments as per protocol *
20. Complete company- specific log (if applicable)
21. Other (specify)_____
22. Other (specify) _____

*These tasks may only be performed by qualified individuals as permitted by local law, medical or standard of care practices, or applicable required training as per job description or designation.

29. Safety Monitoring Register Template

- UNSW Safety Monitoring Register Template
- UNSW Adverse Event or Incident Event Case Report Form Example.

30. Corrective and Preventive Action Form

Raised by:	Assigned to:	Date:	Remarks:
Description:			
Proposed immediate action (correction):			
Completed by:	Date:	Remarks:	
Root cause analysis required: Yes ☐ No ☐			
Underlying / root cause:			

Determined by:	Date:	Remarks:
Proposed action for long term solution (corrective/preventive action):		
Completed by:	Date:	Remarks:
Comments on effectiveness of action taken:		
Closed out by:	Date:	Remarks: