School of Optometry and Vision Science

CLINICAL TRIAL PROTOCOL

Protocol Title - Long:	The Effect of Manuka Eye Drops on Tear Film Properties
Protocol Title - Short:	The effect of Manuka eyedrops on the tear film
Protocol ID Number:	SOVS2018-501
Amendment Number:	N/A
Version Date:	21st March 2018

CONFIDENTIALITY

APPROVALS

[redacted] **Date**

[redacted] **Date**

SPONSOR	
Sponsor:	University of New South Wales (UNSW)
Address:	Sydney, NSW 2052 Australia

SUMMARY OF FINAL PROTOCOL & AMENDMENTS			
Initial/ Amend #	**Version Date**	**Author**	**Main Changes**
Final	**21 March 2018**	[redacted]	N/A
A1			
A2			
A3			

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1. PROTOCOL SYNOPSIS

Table 1: Protocol synopsis

Protocol Title	The Effect of Manuka Eye Drops on Tear Film Properties	
Protocol ID Number	SOVS2018-501	
Trial Classification	Evaluation	
Investigator(s)/Site(s)	Eye Research Group @ SOVS The University of New South Wales Sydney, Australia	
Overall Duration of Trial	4 months	
Number of Trial Participants Planned	48	
Planned Start Date	June 2018	
Primary Objective	To compare the effect on tear film properties and dry eye signs and symptoms of Optimel Manuka eye drops compared to Systane Ultra tear supplement after one month of daily use.	
Secondary Objectives	• To compare the effect on ocular signs and symptoms.	
Primary Safety Variable(s)	Visual acuity Biomicroscopy: ocular redness, corneal details and staining	
Primary Efficacy/Performance Variable	Lipid layer thickness, tear evaporation rate and fluorescein tear breakup time up	
Experimental design	☐ Retrospective ☒ Prospective ☒ Single group ☐ Multiple group ☐ Parallel group ☐ Cross over ☐ Contralateral	☐ Single masked (Trial Participant) ☐ Single masked (Investigator) ☒ Double masked ☐ Sponsor masked ☐ Open label ☒ Other: randomised
Study product details - test	**Name**	Optimel™ Manuka+™ Dry Eye Drops
	Manufacturer	Melcare Biomedical Pty Ltd
Study product details - control	**Name**	Systane Ultra
	Manufacturer	Alcon Laboratories
Inclusion criteria	○ Able to read and comprehend English and give informed consent as demonstrated by signing a record of informed consent; ○ General population aged 18 years and over; ○ In good general health; ○ Subjectively experiencing dry eye symptoms (e.g. burning, irritation, and discomfort due to dryness of the eye or exposure to wind or sun). Participants will be selected based on a minimum OSDI score of 13 points (1). ○ Willing to discontinue CL wear for 1 week before first visit and continue to do so until the conclusion of the study; ○ Participant is willing to discontinue their use of any previous conventional dry eye treatment method commenced before the study throughout the study; ○ Willing to comply with the dosage and study visit schedule as directed by the investigator; ○ No planned changes to diet and willing not to substantially alter	

	their usual diet for the duration of the study, including their typical intake of fish, green tea or oral supplements known to have anti-inflammatory properties; ○ Willingness to notify the study investigator if instructed to alter their diet by health/medical practitioner.
Exclusion criteria	○ Allergy to benzoic acid preservatives; ○ Allergy to honey products; ○ Active anterior eye disease/ infection, inflammation/allergy that requires ocular medical treatment; ○ Eye injury or surgery in the past 6 months including chemical burns, penetrating injuries, traumatic iritis, orbital fractures, laser surgery, strabismus surgery, cataract or any other intraocular surgeries; ○ Soft contact lens, rigid gas permeable, orthokeratology lens wearer within one week prior to the study and during the study. ○ Use of any of the following medications (including steroids) up to 12 weeks prior to start of the study or during the course of the study: - Ocular medication, category S3 and above; - Any systemic or topical medications that will affect ocular physiology e.g. anti-acne medications such as Roaccutane and corticosteroid or immunosuppressant medications such as Hydrocortisone, Prednisolone and antihistamine medications such as Claritine; ○ Any systemic disease that may affect ocular health e.g. Graves disease, and auto-immune diseases such as ankolysing spondylitis, multiple sclerosis and systemic lupus erythematosis; ○ Epilepsy or history of migraines exacerbated by flashing, strobe-like lights; ○ The Investigator may, at his/her discretion, exclude anyone else who they believe may not be able to fulfil the study requirements, or if it is believed to be in the participant's best interests.
Human Research Ethics Committee Status / **Regulatory Status**	This trial requires Human Research Ethics Committee approval prior to study initiation, any advertising, and participant consent/enrolment. The study products are commercially available in Australia and are approved by the Therapeutic Goods Administration.

2. INVESTIGATOR(S)

Table 2: List of investigators

Name:	[redacted]
Title:	[redacted]
Site Address:	[redacted]
Telephone:	[redacted]

Name:	[redacted]
Title:	[redacted]
Site Address:	[redacted]
Telephone:	[redacted]

3. MEDICAL EXPERT

Table 3: Medical Expert

Name:	[redacted]
Title:	[redacted]
Address:	[redacted]
Telephone:	[redacted]

4. BACKGROUND INFORMATION

4.1 Product

Optimel Manuka eye drops (MelCare Biomedical Pty Ltd., Australia) is at present the only available manuka based eye drop commercially available in Australia. It is available both as 16% eye drop as well as 98% gel form [1]. Presently, a growing number of studies are exploring ocular benefits of the drop, based on extensive evidence of antimicrobial, antioxidant, and anti-inflammatory effects of Manuka honey [2-4].

Systane Ultra lubricant eye drops (Alcon Laboratories, Inc., Forth Worth, Tx) is a new generation ocular lubricant that has been developed with a unique intelligent delivery system for the treatment of dry eye symptoms.[5, 6] It is an aqueous solution composed of polyethylene glycol (0.4%) and propylene glycol (0.3%) as demulcents and incorporates the benefits of hydroxypropyl guar as gelling agent.

4.2 Summary

This study is potentially significant in its demonstration of the benefits of Manuka honey eye drops in altering the physiological properties of the tear film, thereby improving ocular comfort and reducing dry eye. These findings will aid in informing practitioners about the benefits of considering Manuka eye drops in the alleviation and treatment of dry eye disease, whilst adding credibility to the Optimel Manuka eye drops range and growing its potential market opportunities globally.

4.2.1. Risks and Benefits

Risks of the Clinical Trial

Although unlikely, it is possible that participants may be allergic to any of the ingredients in the study eye drops. Signs of ocular allergy include swelling, redness, itching and watering of the eyes. Subjects with a known allergy to the study eye drops will not be enrolled. Subjects who experience an allergic reaction will be treated by thoroughly rinsing the eye with preservative free unit-dose saline, continuous monitoring until ocular signs and symptoms have returned to normal, and immediate discontinuation from the study. Subjects may also be referred to the Sydney Eye Hospital for treatment, if required.

Benefits of the Clinical Trial

There is no guarantee or promise that the participants will receive any benefits from this clinical trial.

4.2.2. Treatment Rationale

This is a prospective, randomized, double-masked, single centre study. All eligible participants were randomized into one of the treatment groups. One group received Optimel Manuka eye drops (Leptospermum spp. honey 160 mg/g, water, sodium chloride, benzoic acid 0.2 per cent) (Optimel 16 percent), (Melcare, Australia) and the other group received a non-lipid based conventional ocular lubricant, Systane Ultra (Polyethylene Glycol 400 0.4%, Propylene Glycol 0.3%, aminomethylpropanol, boric acid, hydroxypropyl guar, POLYQUAD® (polyquaternium-1) 0.001% preservative, potassium chloride, purified water, sodium chloride, sorbitol)(Alcon

Laboratories, USA). Participants were asked to instill one drop into each eye, three times a day for twenty-eight days (±4 days).

4.2.3. Guidelines and Regulations

The clinical trial will be conducted in accordance with the protocol, the Declaration of Helsinki (see Appendix 1), ICH GCP and local regulations as applicable including TGA and NH&MRC guidelines.

4.2.4. Trial Population

Thirty-eight (38) participants aged 18 years or above who were assessed to have mild to severe dry eye are required to complete the study. Taking into consideration a 20% drop out rate, approximately 48 subjects will be enrolled in this study.

5. TRIAL OBJECTIVES AND CLINICAL HYPOTHESIS

5.1. Trial Objective

To compare the effects of Optimel Manuka eye drops and Systane Ultra on symptomology assessed using the OSDI questionnaire, and objective tear film properties such as lipid layer thickness and tear break-up time will be measured 4 weeks after use of treatment drops in dry eye participants.

5.2. Clinical Hypothesis

We hypothesize that the:

- Measurable differences in the subjective symptomatology and in objective tear film parameters will be apparent after 4 weeks of use with the Optimel Manuka and Systane Ultra eye drop treatments.

6. TRIAL DESIGN

This will be a prospective, randomized, single centre, double-masked, randomized dispensing study. There will be 2 visits in total:

(i) **Baseline (Week 0)**: Screening, randomization, informed consent, habitual visual acuity, OSDI, symptom survey, biomicroscopy, tear film assessment and dispensing eye drops.

(ii) **28 days of treatment ± 4 days (Week 4)**: habitual visual acuity, OSDI, symptom survey, biomicroscopy, tear film assessment and study exit.

Standard ocular examination and non-standard ocular examination procedures will be carried out at the scheduled visits.

Standard optometric procedures at each visit include:

- Habitual visual acuity
- Slit lamp evaluation including corneal details
- Subjective questionnaire: Ocular Surface Disease Index (OSDI)
- Tear breakup time
- Tear lipid layer thickness

Non-standard optometric procedures may include:

- Tear evaporation rate

6.1. Methodology / Study Visits

6.1.1. Data Requirements per Visit

This study requires 2 visits of approx. 1-hour duration each. The data requirements for each visit are shown in Table 4.

Table 4: Data requirements

Procedures/ Data (Y/N)	**Visit 1** Screening / Baseline	**Visit 2** 28 days ± 4 days
Informed Consent	Y	N
Meet Inclusion/Exclusion Criteria	Y	N
Ocular and Medical History, Medications, Demographics	Y	Y
Vision Tests (Visual Acuity)	Y	Y
Randomization (to eye drop)	Y	N
Slit-Lamp Biomicroscopy	Y	Y
Subjective questionnaire	Y	Y
Tear evaporation rate	Y	Y
Tear break-up time	Y	Y
Tear lipid layer thickness	Y	Y

6.1.2. Randomisation and Masking

Prior to initiation of study treatment, each subject who provides informed consent will be assigned to a subject number that will serve as the subject identification number on all study documents. Subject numbers will be assigned in ascending order and should not be omitted or reused.

Participants will be randomly assigned to the eye drop type to be dispensed (Optimel Manuka+ 16% eye drops or Systane Ultra eye drops). A randomization scheme will be prepared in advance.

The Investigator will provide instructions to the study participants as to the drop instillation technique but will not be cognizant to the randomisation schedule and will not be present during the drop dispensation to maintain masking.

6.1.3. Clinical Trial Population

A total of 46 participants with dry eye disease will be required to complete the study.

Trial participants will be recruited from the local population at the investigational site. An e-mail invitation will be circulated to [redacted]. Advertisements may also be posted in [redacted].

6.1.4. Trial Duration

This study requires 2 visits of approx. 1-hour duration each. The study duration for each participant will be approximately 28 days.

6.1.5. Enrolment

A study participant is considered enrolled when they have signed the Participant Information Statement and Consent Form.

6.2. Primary Endpoint

The primary endpoint is a measurable difference in tear lipid layer thickness between Optimel Manuka eye drops and Systane Ultra eye drops after 4 weeks of daily use.

6.3. Secondary Endpoint(s)

The secondary endpoints are: a measurable difference in tear parameters such as tear breakup time and tear evaporation rate, and subjective symptoms after 4 weeks of daily use.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

7.1. Participant Selection

Participants with dry eye disease will be enrolled. Informed consent will be obtained prior to any clinical trial procedures being conducted. All participants will conform to the clinical trial entry criteria listed below:

7.1.1. Inclusion Criteria

- Able to read and comprehend English and give informed consent as demonstrated by signing a record of informed consent;
- Adults aged 18 years and over with symptoms of dry eye;
- Ocular Surface Disease Index score of >12 at Screening;
- Not wearing contact lenses for 1 week prior to the study and for the duration of the study;
- Willing to use the study eye drops and refrain from using any other eye drops for the duration of the study;
- Willing to refrain from using the study eye drops within 4 hours prior to each study visit;
- Willing to comply with the study visit schedule and adhere to instructions as directed by the Investigator.

7.1.2. Exclusion Criteria

- Any active anterior segment disease excluding blepharitis;
- Use of any of the following medications (including steroids) up to 12 weeks prior to start of the study or during the course of the study:
    - Ocular medication, category S3 and above;
    - Any systemic or topical medications that will affect ocular physiology e.g. anti-acne medications such as Roaccutane and corticosteroid or immunosuppressant medications such as Hydrocortisone, Prednisolone and antihistamine medications such as Claritine.
- Use of any polyunsaturated fatty acid-containing dietary supplements (such as fish oil, evening primrose oil, linseed oil) for less than 12 weeks prior to the start of the study;
- Planned changes to intake of polyunsaturated fatty acid-containing dietary supplements and/or diet (including typical intake of fish) for the duration of the study;
- Use of any at-home eyelid warming treatments for less than 12 weeks prior to the start of the study, or planned changes to routine usage over the course of the study;
- Use of any of the following dry eye treatments up to 6 months prior to the start of the study or during the course of the study:
    - Intense Pulsed Light (IPL) therapy;
    - Blephasteam;
    - LipiFlow Thermal Pulsation treatment;
    - Punctal plugs.
- Any systemic disease that may affect ocular health e.g. Graves disease, and auto-immune diseases such as ankylosing spondylitis, multiple sclerosis and systemic lupus erythematosus;
- History of eye surgery within 6 months prior to enrolment in the study;

- Epilepsy or history of migraines exacerbated by flashing, strobe-like lights;
- Any known allergy to the ingredients in Systane Complete;
- Pregnancy or breastfeeding.

7.2. Participant Withdrawal

Participants may be permanently discontinued from the clinical trial for any of the following reasons:

- If, in the Investigator's opinion, it is in the best interest of the participant;
- Persistent clinical trial-related symptoms/complaints that are not correctable;
- Has a serious adverse event/serious adverse event that is eye related and/or which, in the Investigator's opinion, requires withdrawal of the participant;
- Participant voluntarily withdraws consent from the clinical trial (i.e. Revocation of Consent);
- If a participant is not compliant with the clinical trial requirements and instructions;
- Protocol violations/deviations.

7.3. Withdrawal and Follow-up Procedure

This study comprises four visits for each participant. Any participants who wish to be withdrawn from the study will be exited upon request.

7.4. Early Termination of Trial

The trial may be stopped early for any one or more of the following reasons:

- If the monitoring of the clinical trial reveals unacceptable levels of adverse events, even though some of the participants may not be affected;
- If the Investigator does not adhere to the protocol or decides to stop the study for any reason, with appropriate notification.

In the event of early termination of the trial, the HREC will be notified.

8. NUMBERING

Participant numbering will occur sequentially commencing with '01'.

9. EQUIPMENT TO BE USED / STANDARD & NON-STANDARD PRACTICE PROCEDURES

9.1. Standard Equipment and Procedures:

- ***Visual Acuity:*** Measurement of the standard of vision achieved with spectacles using standard letter charts. Measurements are taken under monocular and/or binocular conditions.
- ***Slit-Lamp Biomicroscopy:*** A specialised microscope with its own light source is used to examine the anterior eye.
- ***Subjective questionnaire:*** The "ocular surface disease index" questionnaire will be administered. This consists of 12 questions relating to the participant's dry eye symptoms.
- ***Lipid layer thickness:*** The LipiView® Ocular Surface Interferometer (TearScience®) measures the absolute thickness of the tear film lipid layer by analyzing more than one billion data points of the interferometric image of the tear film. The patient's eye is positioned in front of an illumination source that is directed toward the tear film on the corneal surface. Light from this source passes through the tear film and is specularly reflected into a camera. The camera records a 20-second video of the tear film interference and subsequently displays a value in interferometric colour units (ICUs) where 1 ICU approximates 1 nm of lipid layer thickness.
- ***Tear Break-Up Time*:** Following instillation of fluorescein, tear break up time will be measured.
- ***Fluorescein Assessment:*** The ocular surface is assessed by instilling a harmless fluorescent dye called 'fluorescein' directly to the inferior bulbar conjunctiva using a sterile strip impregnated with fluorescein and moistened with sterile saline. The eye is assessed with the slit-lamp biomicroscope using a cobalt blue filtered light and a Wratten 12 filter.

9.2. Non-Standard Equipment and Procedures:

Non-standard procedures that may be performed include:

- ***Tear evaporation rate:*** The Vapometer is a closed chamber device which is used for measuring transepidermal water loss. Participants will be seated upright on a chair and provided with a distance fixation target. To minimize the effect of skin evaporation, petroleum jelly (Vaseline_, http://www.unilever.com.au/brands-in-action/detail/Vaseline/299339/) will be applied over the upper eyelid and the surrounding areas. The VapoMeter will then be placed over the eye and a non-invasive measurement of tear evaporation will be taken within 10 seconds. Participants will be instructed not to blink during open eye measurement and to maintain a normal straight gaze at the fixation target. Evaporation rates with the eyes closed will also be taken, in order to account for the skin evaporation from eyelids and surrounding skin tissue.

9.3. Maintenance and Calibration of Equipment

Equipment will be monitored regularly for maintenance and calibration as per relevant company and product manuals.

10. TREATMENT OF PARTICIPANTS

10.1. Administration of drops

The Investigator will provide instructions to the study participants as to the drop instillation technique but will not be cognizant to the randomisation schedule and will not be present during the dispensing of the drops to maintain masking.

10.2. Drop Storage and Accountability

10.2.1. Storage Requirements

Drops will be stored at room temperature in a secure storeroom/cupboard. The storage facility should be kept locked to prevent unauthorized access and to ensure accountability of the study lenses at all times.

10.2.2. Accountability

An Eye Drop Tracking spreadsheet is used for keeping track of who, where and when drops have been issued or dispensed to.

- ***Receipt of drops:*** Once invoice has been checked, the drops will be entered into the Eye Drop Tracking spreadsheet.
- ***Issue of Drops to Clinical Trial Participants:*** The Optometrist is responsible for documenting the dispensing of the drops on the Eye Drop Tracking spreadsheet.
- ***Disposal of Unused Supplies:*** Instruction will be obtained from the Sponsor as to how to handle returned, unused drops.

10.3. Concomitant Therapy

Whilst participating in this clinical trial participants are not permitted to enrol in other clinical trials.

Participants must not use or have a need for any systemic or topical medications which may alter normal ocular findings/are known to affect a participant's ocular health/physiology either in an adverse manner or risk providing a false positive.

Participants will be instructed to refrain from wearing contact lenses for 1 week prior to the study and for the duration of the study.

10.4. Participant Instructions

<u>General instructions to all participants</u>
Contact the clinic immediately if problems are experienced or if they have any questions or concerns.

11. ASSESSMENT OF EFFICACY

11.1. Parameters

A measurable difference in subjective symptoms and/or objective tear lipid layer thickness or tear breakup time between Optimel Manuka eye drops and Systane Ultra Eye drops after 4 weeks of daily use.

11.2. Methods

Subjective symptoms will be measured using the OSDI questionnaire.

Tear film inferior lipid layer thickness (LLT; nm) will be measured using the LipiView II (Johnson and Johnson Vision, USA). The participant's eye is positioned in front of an illumination source that is directed toward the tear film on the corneal surface. The camera records a 20-second video of the tear film interference and subsequently displays a value in interferometric colour units (ICU), where 1 ICU approximates 1nm of lipid layer thickness.

Fluorescein tear break-up time (TBUT; sec) (Opti-Strip-FL, Optimed, Lane Cove West, NSW, Australia) was measured viewed with a yellow Wratten filter (No. 12, Kodak) and cobalt light of the slit lamp biomicroscope. Three consecutive TBUT measurements for each eye were taken by a single masked investigator.

12. ASSESSMENT OF SAFETY

12.1. Parameters

- Visual acuity
- History
- Ocular health
- Corneal staining

12.2. Methods

Visual acuity will be measured using standard letter charts. The study participant's habitual visual acuity will be assessed.

History (including medical and general health) will be recorded at the study visit.

Slit lamp biomicroscopy will be assessed to evaluate ocular surface health.

An optometrist will be available for the duration of the study. Participants will be advised to contact the Optometrist immediately of any event not normal e.g. unusual redness, pain, irritation, etc. At the clinic, the Optometrist will briefly assess the eye on a slit-lamp under low illumination to ascertain the nature of the condition, if any. If an adverse event occurs, the appropriate procedures will be conducted, including referral for medical treatment if necessary. Any adverse events will be followed until complete resolution to the reasonable satisfaction of the participant and the investigator.

12.3. Definitions

12.3.1. Adverse Events

Adverse Event: Any undesirable clinical occurrence in a participant, that includes a clinical sign, symptom or condition and/or observation of an unintended technical performance or performance outcome.

Adverse Events may be classified as Serious, Significant, Non-significant or Unanticipated as defined further on.

12.3.2. Serious Adverse Events

Any adverse medical occurrence that:

- led to death.
- led to a serious deterioration in health of a Participant user or other. This would include:
    - a life threatening illness or injury.

  - a permanent impairment of body function or permanent damage to a body structure.
  - a condition requiring hospitalisation or increased length of existing hospitalisation.
  - a condition requiring unnecessary medical or surgical intervention.
  - foetal distress, foetal death or a congenital abnormality/birth defect.
- might have led to death or a serious deterioration in health had suitable action or intervention not taken place.

Specifically for the eye, Serious Adverse Events include but are not limited to:

- permanent decrease in best-corrected visual acuity (≥2 lines)
- central corneal opacities
- central corneal neovascularisation – in the central 4mm of the cornea
- central corneal opacities – in the central 4mm of the cornea
- infectious corneal ulcers
- uveitis
- iritis
- endophthalmitis
- hypopyon
- hyphema
- penetration of bowman's membrane
- persistent epithelial defect
- limbal cell damage leading to conjunctivalisation.

Serious adverse events are reportable.

12.3.3. Significant Adverse Events

Significant Adverse Events are those that are symptomatic (excluding serious adverse events noted above). They include, but are not limited to:

- ***Infiltrative keratitis:*** Inflammatory reaction of the cornea characterised by anterior stromal infiltrates with or without epithelial involvement. Symptoms include mild to moderate irritation, and redness. Staining may be slight to moderate.

- ***Conjunctivitis:*** Inflammatory reaction of the conjunctiva characterised by discharge, grittiness, redness and swelling.

- ***Corneal Erosion:*** Full thickness epithelial loss over a discrete area.

12.3.4. Non-Significant Adverse Events

Non-significant Adverse Events are those that treatment, if needed, is usually with over the counter products. They include, but are not limited to:

- asymptomatic infiltrative keratitis
- blepharitis
- meibomitis
- contact dermatitis
- localised allergic reactions.

12.3.5. Unanticipated Adverse Events

Adverse events or serious adverse events are considered “unexpected” or “unanticipated” if they do not appear listed in the technical manuals to date. These events require expedited reporting.

12.3.6. Event Severity

Events should be rated by a study investigator according to their severity:

Mild: No treatment required
Moderate: Treatment required.
Severe: Requires referral to and treatment by an ophthalmologist.

12.4. Reporting

In the event of persistent irritation, redness, reduced visual acuity or any other unusual signs or symptoms, the participants will be advised to contact the investigators immediately.

Non-serious and anticipated adverse events should be recorded as part of Good Clinical Practice. Sponsors are expected to maintain up-to-date tabulations and/or line listings of all adverse events.

All Serious Adverse Events should be reported to the HREC as per their reporting requirements. This should be followed by a more detailed written report commenting on potential confounding factors, results of investigations, treatment required and outcome.

12.4.1. Expedited Reporting

UNSW, via the Principal Investigator (PI) of the clinical trial is required to report to the Therapeutic Goods Administration (TGA) single cases of serious and unanticipated adverse events.

- ***Fatal or life-threatening unexpected adverse events*** – the TGA should be notified as soon as possible but no later than 7 calendar days after first knowledge by the PI that the case qualifies, followed by a complete report as possible within eight additional calendar days.
- ***All other serious, unexpected adverse events*** – TGA notification as soon as possible but no later than 15 calendar days after first knowledge by the PI that the case meets the minimum criteria for expedited reporting.

In the case of an unexpected and serious adverse event that occurs outside Australia with use of the same product, the TGA and HREC should also be notified. The time frame for this reporting should be within 72 hours of any significant safety issue which has arisen from an analysis of overseas reports or action which has been taken by another country's regulatory agency. This advice must include the basis for such action. Investigators should also be notified, who must in turn notify the HREC.

Reports should be on the 'Medical Incident Report Form' located on the TGA website (http://www.tga.gov.au/docs/html/forms/iris_mdir.htm) or similar format, and clearly marked 'Clinical Trial Adverse Event' and sent to:

[redacted]

12.4.2. Foreseeable Adverse Events

Risks associated with the use of the study eye drops include:

- Eye discomfort/stinging (<30%)
- Eye redness (<10%)
- Blurry vision (<10%)

12.4.3. Other Observations

There may be other situations that may necessitate rapid communication to regulatory authorities. Scientific and medical judgment should be applied for each situation. In general, information that

might materially influence the benefit-risk assessment of a product or that would be sufficient to consider changes in product administration or in the overall conduct of a clinical investigation represent such situations.

12.5. Follow-up

Participants who experience an adverse response will be discontinued from the study and followed up until the condition resolves or the participant is referred to another practitioner.

12.6. Referrals

Participants will be referred to a medical expert when judged by the optometrist to be necessary. After hours, participants will be referred to [redacted] (Table 5).

Table 5: [redacted]

Title:	[redacted]
Address:	[redacted]
Telephone:	[redacted]

13. STATISTICS

13.1. Description

Data stored in relational databases will be imported into SPSS software for statistical purposes. Statistical analysis will initially be reported in Excel. Data will be investigated for quality using range checks and frequency distribution. Underlying distributions of variables will be tested. Details of statistical analysis are described in Section 13.1.3.

13.1.1. Number of Participants

38 participants will be required to complete the study.

13.1.2. Significance

A p-value less than or equal to 5% will be considered to be statistically significant.

13.1.3. Analysis

Participants who complete the study treatment will be included in the analysis dataset. Reasons and frequency distribution of participants discontinued will be reported.

Data will be summarised as means ± standard deviations for variables measured on an interval scale and median ± inter-quartile range for ordinal variables. Statistical tests will be employed to determine significant differences in tear parameters, subjective symptoms and other parameters between Optimel Manuka+ Eye Drops and Systane Ultra eye drops. Normality will be assessed using the Shapiro-Wilk test. Independent t-tests will be used for comparison of continuous normally distributed data between the test and control groups. Non-parametric data will be analysed using Mann-Whitney U test. Proportions will be compared using $\chi 2$ tests and associations will be examined using Pearson's correlation. The level of significance is set at alpha=0.05. Statistical analysis will be performed using SPSS software V.22.0. The difference between the 28 days and baseline data will be used to quantify the treatment effect.

13.2. Criteria for Termination of the Trial

The trial will be terminated upon completion of the final study visit by the last participant or unless any of the conditions of Section 7.4 are met. An active participant is one who is enrolled in the study and has not been discontinued.

13.3. Accountability of Data

Individual data points that are missing will be excluded from analysis involving only those specific variables. A participant's complete visit data will not be excluded if some of the observations are missing. Inclusion of outliers in the analysis will be based on the magnitude of change in test statistic with and without the outliers. Outliers will preferably be retained unless there is significant change in test results.

14. DATA HANDLING AND RECORD KEEPING

14.1. Source Data

The Investigator/Institution is to maintain the trial documents as specified in ICH GCP guidelines and as required by the applicable local regulations. The Investigator/Institution is to also take measures to prevent accidental or premature destruction of clinical trial-related documentation.

Paper Case Report Forms will be utilized for this clinical trial, and will be entered into Excel spreadsheets for importing into statistical software. For tests conducted that produce printed results, these should be included in the participant's file. Source data includes, but is not limited to printouts, diagrams, videos, photos, and any other paper, electronic or digital data that is the first recording of that information, and these must be maintained by the Investigator in the source files for the participant, or if unable to file (e.g. digital images), then reference should be made to their location. The clinic records will maintain a record of trial participation but will not be considered as the source.

14.2. Direct Access to Source Data/Documents

The Investigator will conduct this clinical trial under HREC review. As necessary the Investigator will provide the HREC and appropriate regulatory authorities direct access to source data/documents for review.

14.3. Data Management

The data will be accessible to study personnel only, secured and backed up regularly.

14.4. Data Archiving

Electronic data will be stored in a secure off-site storage facility. Paper records are archived approximately 3 months after study closeout. The records are initially kept on site in a secure location, and may later be transferred to a secure off-site storage facility.

14.5. Retention of Essential Documents

The Investigator/Institution is to retain essential documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region. However, these documents should be retained for longer if required by local regulatory agencies.

The Investigator/Institution must also retain essential documents for 15 years as per TGA requirements following the completion of a clinical trial. However, essential documents may need to be retained longer after consideration of the following: product liability and the potential need to produce records at any time during, and possibly beyond, the life of a product in the event of a claim as a result of an adverse outcome associated with the use of the product.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Ethical Considerations

This trial requires HREC approval prior to start.

The Investigator is to ensure that the protocol, Participant Information Statement and Consent Form, available safety information, information about payment and compensation to participants, advertising or any clinical trial specific information provided to participants (including potential participants), the Investigator's CV and/or evidence of appropriate qualifications and any other documentation they may request are submitted, reviewed and approved. Any subsequent amendments will be reviewed and approved by an HREC prior to implementation.

The HREC must be appropriately constituted, and will perform its functions in accordance with the applicable local regulatory requirements (TGA and NHMRC) and GCP.

This trial will be conducted in accordance with local guidelines and requirements (including those of the NHMRC and TGA, as applicable).

15.1.1. Confidentiality

Confidentiality will be maintained throughout the clinical trial by all parties involved in accordance with guidelines under section 95 of the Privacy Act 1998, and guidelines approved under section 95a of the Privacy Act 1998 (December 2001). Data will be secured against unauthorised access.

Privacy and confidentiality of information about each clinical trial participant will be preserved in the reports and any publication of the clinical investigation data.

15.1.2. Informed Consent

The nature and purpose of the trial will be fully explained to each participant. Written informed consent must be obtained from each participant prior to any trial procedures being performed.

The informed consent documentation to be used for the trial will include all the elements of informed consent per GCP, and TGA requirements as applicable, and will be reviewed and approved by the HREC prior to use.

15.1.3. Protocol Amendments

The Investigator will review deviations to determine the need to amend the protocol or to terminate the investigation. Justification for any changes will be provided.

Protocol amendments will be submitted to the HREC for review and approval prior to implementation, unless the change required is to eliminate an immediate hazard to trial participants, or involves only administrative and/or logistical aspects of the trial (e.g. Change in contact numbers).

15.1.4. Investigator Responsibilities

The Investigator is responsible for ensuring participant safety and data quality by: protocol compliance, adherence to GCP and local regulatory requirements, and the Declaration of Helsinki. The Investigator should be appropriately qualified and legally entitled to practice, and be trained in the proper method of obtaining informed consent.

The Investigator must have the appropriate resources to conduct the clinical trial, be familiar with the protocol and agree to adhere to it, support monitoring and auditing activities, make the necessary arrangements to ensure proper conduct and completion of the clinical trial, and ensure the protection and welfare of the participant, including arranging any emergency treatment as needed.

The Investigator must ensure written HREC approval is received prior to the start of the clinical trial, that the HREC is kept informed of the clinical trial progress, including serious/adverse events and deviations as required by them, and that any changes to the protocol are notified to the HREC and receive written approval prior to implementation.

The Investigator must try to ensure adequate participant recruitment; that all necessary and appropriate information is given to potential participants to ensure informed consent; to ensure informed consent is taken and documented; and that clinical records indicate the participant is enrolled in a clinical trial. The Investigator must ensure that clinical trial participants are provided with emergency contact details along with a procedure to follow in the case of an emergency, and that clinical trial participants are kept informed as pertinent new information becomes available that may affect their decision to participate.

The Investigator has primary responsibility for the accuracy, legibility and security of all clinical investigation data, documents and participant records at the investigator site during and after the clinical trial. Case Report Forms are to be signed by the Investigator, and any alterations to data are to be by authorised personnel, initialled and dated by same.

The Investigator must ensure that data be kept for the minimum time as specified by this protocol, investigational product must be accounted for (the quantity received must be reconciled with the quantities used, discarded or returned), and must also be responsible for the supervision and assignment of duties to all responsible for the conduct and evaluation of the clinical trial for the investigator centre involved.

16. FINANCING AND INSURANCE

Memorandum of Agreement can be provided on request.

17. PUBLICATION POLICY

Please refer to Memorandum of Agreement.

INVESTIGATOR AGREEMENT

"I agree to conduct the trial outlined above according to the terms and conditions of the protocol, Good Clinical Practice Guidelines and with the applicable regulatory requirements. All information pertaining to the trial shall be treated in a confidential manner."

Principal Investigator's Signature: _____ Date:_____

Principal Investigator's Printed Name: _____

APPENDIX I

DECLARATION OF HELSINKI

APPENDIX I: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association (WMA), the global representative body for physicians.

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

APPENDIX I: Declaration of Helsinki *(cont.)*

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

APPENDIX I: Declaration of Helsinki *(cont.)*

At the conclusion of the study, every patient entered into the study should be assured of access to the best
30. proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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