CLINICAL TRIAL PROTOCOL

Protocol Title - Long:	A two comparator, controlled phase 3 study of OM3 Tear formulation versus OPTIVE ADVANCED Unit Dose and OPTIVE Unit Dose eye drops in patients with and without evaporative dry eye.
Protocol Title - Short:	Omega 3 Tear
Protocol ID Number:	SOVS-2016-040
Amendment Number:	N/A
Version Date:	14th July 2016

CONFIDENTIALITY

APPROVALS

[redacted]	**Date**
[redacted]	**Date**
[redacted]	**Date**
[redacted]	**Date**

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

CO-SPONSOR	
Sponsor:	[redacted]
Address:	

SUMMARY OF FINAL PROTOCOL & AMENDMENTS

Initial/ Amend #	Version Date	Author	Main Changes
Final	**14th July 2016**	[redacted]	N/A
A1			
A2			
A3			

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1. PROTOCOL SYNOPSIS

Table 1

Protocol Title	A two comparator, controlled phase 3 study of OM3 Tear formulation versus OPTIVE ADVANCED Unit Dose and OPTIVE Unit Dose eye drops in patients with and without evaporative dry eye.
Background	○ The normal tear film is a relatively stable, thin film composed of a superficial lipid layer and an aqueous layer intermixed with a mucous gel layer, which is partially adherent to the corneal and conjunctival surface epithelium ○ Dysfunction of one or more components of the tear film can lead to loss of tear film stability and symptoms of dry eye ○ The majority of patients with dry eye are prescribed artificial tears to alleviate symptoms and maintain a healthy ocular surface ○ OM3 Tear is a new unit dose emulsion, containing flaxseed/castor oil, which is being developed by [redacted]. It is desirable to understand the effect that this new emulsion has on tear film evaporation and tear lipid profile via interferometry, in patients with evaporative dry eye (EDE) and those without (non-EDE). It would also be valuable to evaluate the retention time of the lipid components of the new emulsion via tear collection and analysis in EDE and non-EDE patients
Study Design	Single centre, double-masked, randomized, 3 arm comparison of OM3 Tear eye drops to two comparators.
Aims and Objectives	To measure tear film evaporation rate, tear lipid profile via interferometry and tear lipid components before and 15 mins, 1 hour and 4 hours after the first dose, and again after 4 weeks of use of the emulsion OM3 Tear eye drops, compared to two comparators (Optive Advanced Unit Dose and Optive Unit Dose).
Recruitment	September 2016
Study Start & End Dates	September 2016 – April 2017
Sample size	Up to 40 participants will be recruited (approx. 20 EDE and 20 non-EDE subjects). This sample size was calculated on the basis of detecting a difference in: ○ tear evaporation rate between the eye drops of 36 gm^{-2}/h where the expected standard deviation of the measurement is 50 gm^{-2}/h, assuming an estimate of type 1 error α =0.05 and power of 80% for a two tailed test[1]
Subject Source	UNSW and general community

Selection criteria	*General Inclusion Criteria* o Able to read and comprehend English and give informed consent as demonstrated by signing a record of informed consent; o Over 18 years of age; o Not wearing contact lenses in the past 3 months before enrolling o Willing to use eye drops and comply with the study visit schedule as directed by the Investigator; o Habitual (corrected or uncorrected) visual acuity of 6/9.5 or better in each eye; o At the Screening visit (Day -14), patients must have Ocular Surface Disease Index (OSDI) score >18 (0 to 100 scale). At Baseline (Day 1) visits, patients must have OSDI score > 12 to continue in the study. o TBUT≤10sec in at least 1 eye at Screening visit and Baseline visit o Corneal sodium fluorescein staining score ≥ 1 and <4 (Oxford scheme) at Screening and Baseline visit. *Additional Inclusion Criteria for <u>EDE</u> Classification* o Tear Evaporation Rate (TER) ≥ 110 - To be confirmed (TBC) *Additional Inclusion Criteria for <u>non-EDE</u> Classification* o Tear Evaporation Rate (TER) < 110 (TBC) For patients who have one eye meeting EDE criteria, and other eye meeting non-EDE criteria, their Schirmer score will be used to determine the classification. If their Schirmer score is >10 in both eyes, they will be classified in the EDE group. *General Exclusion Criteria* o Schirmer test (with anesthesia) ≤ 2 mm in either eye at Screening o Patients who are currently using topical ocular medication or have used topical ocular medication within 2 weeks of the Screening visit. Patients who are being treated bilaterally with a marketed artificial tear for dry eye can be considered, provided they discontinue use at the Screening visit; o Any active anterior segment disease <u>excluding</u> blepharitis; o 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; o History of epilepsy or migraines exacerbated by flashing, strobe-like lights; o Rigid or soft contact lens wearer, including orthokeratology; o History of eye surgery within 6 months prior to enrolment in the study; o Previous corneal refractive surgery.
Visit Schedule – 3 arm study	Visit 1 (Day -14): Screening visit, dispensing run-in product (Refresh Plus) **ARM 1:** Visit 2a (Day 1): Pre-instillation and 15 min (± 5 min) post-instillation assessment - Eye Drop #1 Visit 2b (Day 1): 1 hour (± 15 min) post-instillation assessment - Eye Drop #1 Visit 2c* (Day 1): 4 hour (± 30 min) post-instillation assessment - Eye Drop #1 Visit 3 (4 weeks): 4 week assessment - Eye Drop #1 **ARM 2:** (after minimum 2 week wash-out period using run-in product Refresh Plus)

	Visit 4a ([6 weeks): Pre-instillation and 15 min (± 5 min) post-instillation assessment - Eye Drop #2 Visit 4b (6 weeks): 1 hour (± 15 min) post-instillation assessment - Eye Drop #2 Visit 4c* (6 weeks): 4 hour (± 30 min) post-instillation assessment - Eye Drop #2 Visit 5 (10 weeks): 4 week assessment - Eye Drop #2 **ARM 3:** (after minimum 2 week wash-out period using run-in product Refresh Plus) Visit 6a (12 weeks): Pre-instillation and 15 min (± 5 min) post-instillation assessment - Eye Drop #3 Visit 6b (12 weeks): 1 hour (± 15 min) post-instillation assessment - Eye Drop #3 Visit 6c* (12 weeks): 4 hour (± 30 min) post-instillation assessment - Eye Drop #3 Visit 7 (16 weeks): 4 week assessment Eye Drop #3 Note: Subjects are NOT to instil any eye drops within 3 hours prior to the scheduled visits * 4 hour assessments will only be conducted on participants who are able to attend this additional visit on the same day as the initial assessment
Procedure	Standard ocular examination and non-standard ocular examination procedures will be carried out at the scheduled visits. *Standard optometric procedures may include*: o Subjective questionnaires (OSDI, Likert and VAS) o Corneal and conjunctival staining (Fluorescein and Lissamine Green) *Non-standard optometric procedures may include*: o Tear evaporation rate (Modified Vapometer, Delphin Technologies) o Tear Break-Up Time (with fluorescein) and lipid layer grade o Tear film lipid layer thickness (LipiView Interferometer) o [redacted]
Study Endpoints	The primary endpoint is a measurable difference in tear evaporation rate between the eye drops after initial application (15 min) and/or after 1 hour and/or 4 hours of application and/or after 4 weeks of daily use. The secondary endpoints are (i) a measurable difference in TBUT between the

	eye drops after initial application (15 min) and/or after 1 hour and/or 4 hours of application and/or after 4 weeks of daily use and (ii) a measurable difference in symptom improvement between the eye drops after initial application (15 min) and after 4 weeks of daily use.
Statistical Considerations	Paired t-tests, repeated measures ANOVA or linear mixed model analysis using Bonferroni adjustment for multiple comparisons and p value set at $p<0.05$. Mann Whitney U test will be used to compare tear film lipidome between the eye drops.
IRB Status & Details	This clinical research study requires approval from the Human Research Ethics Committee at the University of New South Wales prior to study initiation, any advertising, and participant enrolment. o HREC meetings held monthly o Lead time for new applications: approx. 2 months
Dissemination of Results	o Publication in peer-reviewed journals o Presentation at International conferences

2. INVESTIGATOR(S)

Table 2

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

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

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

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

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

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

3. MEDICAL EXPERT

Table 3

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

4. BACKGROUND INFORMATION

4.1. Background and Clinical Rationale

The normal tear film is a relatively stable, thin film composed of a superficial lipid layer and an aqueous layer intermixed with a mucous gel layer, which is partially adherent to the corneal and conjunctival surface epithelium. Dysfunction of one or more components of the tear film can lead to loss of tear film stability and symptoms of dry eye. The majority of patients with dry eye are prescribed artificial tears to alleviate symptoms and maintain a healthy ocular surface.

The purpose of this study is to evaluate the retention time of the lipid components of the new emulsion OM3 Tear eye drops via tear collection and analysis in evaporative dry eye (EDE) and non-EDE patients. Tear film evaporation rate, tear lipid profile via interferometry and tear lipid components will be evaluated before and 15 mins, 1 hour and 4 hours after the first dose, and again after 4 weeks of use of the emulsion OM3 Tear eye drops, compared to two comparators (Optive Advanced Unit Dose and Optive Unit Dose).

4.2. Summary

4.2.1. Risks and Benefits

Risks of the Clinical Trial

It is possible that participants may have an allergic reaction to any the study eye drops. Signs of ocular allergy (e.g. redness, itching and watering) will be treated by immediate discontinuation of use of the study eye drops and participation in the study. However, participants will be monitored until ocular signs and symptoms have returned to normal. Topical and/or oral antihistamines may be prescribed if deemed appropriate. The participant will be referred for appropriate medical treatment if required.

Any potential participants with a self-reported allergy/sensitivity to any of the study eye drops will be excluded from the study.

The Lipiview Ocular Surface Interferometer uses flashing strobe-like lights which may have an adverse effect on participants with a history of epilepsy or migraines. Any potential participants with epilepsy or a history of migraines exacerbated by flashing, strobe-like lights will be excluded from the study.

Benefits of the Clinical Trial

Participants will receive ocular lubricant treatment for their dry eye condition. However, there is no guarantee or promise that the participants will receive any health benefits from this clinical trial. The study eye drops and participants' optometric care will be provided free of charge for the duration of the clinical trial.

4.2.2. 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.

4.2.3. Trial Population

40 participants will be recruited (approx. 20 EDE and 20 non-EDE subjects).

5. STUDY OBJECTIVES AND CLINICAL HYPOTHESIS

5.1. Study Objective

The objective of this study is to measure tear film evaporation rate, tear lipid profile via interferometry and tear lipid components with the use of the emulsion OM3 Tear eye drops, compared to two comparators (Optive Advanced Unit Dose and Optive Unit Dose) in subjects with EDE and those without (non-EDE)

5.2. Clinical Hypothesis

Tear evaporation rate as measured with the Vapometer is better (i.e. lower) with the emulsion OM3 Tear formulation compared to at least one of the two comparators at one or more of the post eye drop instillation time-points.

6. STUDY DESIGN

This study is a single centre, double-masked, randomized, 3-arm comparison of emulsion OM3 eye drops compared to two comparators. All study subjects will attend a Screening visit and receive REFRESH PLUS® for 2 weeks during a run-in period prior to randomization. Subjects will be randomized as to the order of allocation to use the OM3 Tear eye drop and the two comparators. For each arm of the study, assessments will be conducted prior to eye drop instillation and 15 min, 1 hour and 4 hours post-instillation. Subjects will then be dispensed with the randomized study eye drop and instructed to instill 1 to 2 drops of their assigned study product in each eye, as needed, but at least twice daily, for 4 weeks. Subjects will attend a 4 week visit assessment and then undergo a minimum 2 week wash-out period using run-in product REFRESH PLUS® before returning to complete the next arm of the study. These procedures will be repeated until the subjects have completed all 3 arms of the study.

The primary endpoint is a measurable difference in tear evaporation rate between the eye drops after initial application (15 min) and/or after 1 hour and/or 4 hours of application and/or after 4 weeks of daily use.

All proposed procedures conform to the NHMRC Statement on Human Experimentation.

Participants are considered enrolled when they have signed the informed consent form and are regarded as part of the clinical trial population.

6.1. Methodology / Study Visits

6.1.1. Data Requirements per Visit with Visit window (± days)

The data requirements for each visit are shown in Table 4.

Table 4

	Visit 1	*Visit 2a*	*Visit 2b**	*Visit 2c*	*Visit 3a*	*Visit 3b**	*Visit 3c*	*Visit 4a*	*Visit 4b**	*Visit 4c*
Timeline	***Day -14***	***Day 1 #1***	***Day 1 #1***	***4 weeks #1***	***6 weeks #2***	***6 weeks #2***	***10 weeks #2***	***12 weeks #3***	***12 weeks #3***	***16 weeks #3***
Procedure										
Informed Consent	Y	N	N	N	N	N	N	N	N	N
Inclusion/Exclusion criteria	Y	Y	N	N	N	N	N	N	N	N
Ocular, medical history, medications, demographics	Y	N	N	N	N	N	N	N	N	N
Updated history, symptoms, problems	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
Vision tests	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Biomicroscopy (ocular health, staining)	Y	Y	N	Y	Y	N	Y	Y	N	Y
Meibomian gland assessment	Y	N	N	N	N	N	N	N	N	N
Schirmer test (eligibility)	Y	N	N	N	N	N	N	N	N	N
Instill eye drops	Y	Y	N	N	Y	N	N	Y	N	N
Tear evaporation rate	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Eye photo (ocular surface area)	Y	N	N	N	N	N	N	N	N	N
Schirmer test (tear collection)	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
LipiView	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
TBUT (fluorescein)	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
Questionnaires (OSDI, VAS)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y = Yes, required information, N = No, not required
 # = eye drop
a = Baseline and 15 min post-eye drop assessment
b = 3-5 hour post-eye drop assessment
c = 4 week post-eye drop assessment

*Visits 2b, 3b and 4b are scheduled 4 hours (± 30 mins) after the corresponding visits 2a, 3a and 4a on the same day, and therefore are not compulsory for all study participants to attend. Only those who are able to attend this visit will complete the assessment visits 2b, 3b and 4b.

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.

At the Screening visit (Visit 1), all eligible subjects will receive run-in product (REFRESH PLUS) for use during the 14-day run-in period. The clinical site will dispense the run-in product. At the time of randomization (Visit 2, Arm 1), eligible subjects will be randomly assigned to 1 of the 3 treatments. A randomization scheme will be prepared in advance.

Study product will be labeled with study product kit numbers. At Visit 2 (Arm 1), the specific study product kit number for each randomized subject will be dispensed by unmasked administrative study personnel and all study measurements will be conducted by the masked investigator. Unused study product will be returned at the 4 week follow-up visit and the run-in product will be dispensed to be used during the wash-out period. This procedure will be repeated until all arms of the study have been completed.

The emulsion OM3 Tear formulation and the two comparator unit dose eye drops will be provided in similar 0.4 mL unit-dose vials (comparator products will have commercial labeling).

6.1.3. Clinical Trial Population

40 participants (approx. 20 EDE and 20 non-EDE subjects) will be recruited for the study.

Trial participants will be recruited from the local population at the investigational site. [redacted].

6.1.4. Trial Duration

This study is a randomized 3-arm comparison of emulsion OM3 eye drops compared to two comparators. Participants will attend a Screening visit (Day -14) and up to 3 scheduled visits for each eye drop. It will take participants

approximately 18 weeks to complete all 3 arms of the study.

Table 5: Visits

Visit Type:	Visit No:	Study Arm
Screening (Day -14)	1	-
Eye Drop #1: Baseline and 15 min assessment	2a	1
Eye Drop #1: 3-5 hour assessment	2b	1
Eye Drop #1: 4 week assessment	2c	1
Eye Drop #2: Baseline and 15 min assessment	3a	2
Eye Drop #2: 3-5 hour assessment	3b	2
Eye Drop #2: 4 week assessment	3c	2
Eye Drop #3: Baseline and 15 min assessment	4a	3
Eye Drop #3: 3-5 hour assessment	4b	3
Eye Drop #3: 4 week assessment and Exit	4c	3

All study participants will attend a Screening visit and receive REFRESH PLUS® for 2 weeks during a run-in period prior to randomization at Visit 2a. After the 4 week assessment, all study participants will undergo a minimum 2 week wash-out period using run-in product REFRESH PLUS® before returning to complete the next arm of the study. These procedures will be repeated until the subjects have completed all 3 arms of the study.

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 evaporation rate (Vapometer) between the eye drops after initial application (15 min) and/or after 1 hour and/or 4 hours of application and/or after 4 weeks of daily use.

6.3. Secondary Endpoint(s)

Tear break-up time (TBUT) with fluorescein, subjective comfort scores and lipid layer thickness (LipiView).

7. SELECTION AND WITHDRAWAL OF PARTICIPANTS

7.1. Participant Selection

Only subjects who have signs and symptoms of dry eye disease (EDE or non-EDE) will be enrolled.

Participants will be pre-screened for suitability by way of a general phone questionnaire. Informed consent will be obtained prior to any clinical trial procedures.

All participants will conform to the clinical trial entry criteria listed below:

7.1.1. Inclusion Criteria

The following are requirements for entry into the study:

1. Male or female, ≥ 18 years of age;
2. Able to read and comprehend English and give informed consent as demonstrated by signing a record of informed consent;
3. Not wearing contact lenses in the past 3 months before enrolling;
4. Willing to use eye drops and comply with the study visit schedule as directed by the Investigator;
5. Habitual (corrected or uncorrected) visual acuity of 6/9.5 or better in each eye;
6. At the Screening visit (Day -14), patients must have Ocular Surface Disease Index (OSDI) score >18 (0 to 100 scale). At Baseline (Day 1) visits, patients must have OSDI score > 12 to continue in the study;
7. TBUT≤10sec in at least 1 eye at the Screening visit;
8. Corneal sodium fluorescein staining score ≥ 1 and <4 (Oxford scheme) at screening and baseline visit;
9. If using RESTASIS® cyclosporine ophthalmic emulsion, subjects must be using drops for ≥ 3 months prior to Screening.
10. Subjects with primary open-angle glaucoma or ocular hypertension (OHT) may be included provided they are on stable monotherapy bilaterally, with both eyes IOP controlled (≤ 21 mm Hg). Any topical IOP-lowering medications must have a start date of ≥ 3 months prior to Screening date and dosage is not expected to change during the study. The type of medication will be recorded at the Screening visit along with other concomitant medications;
11. Ability to follow study instructions and likely to complete all required visits.

Additional Inclusion Criteria for <u>EDE</u> Classification:

- Tear Evaporation Rate (TER) ≥ 110 (TBC)

Additional Inclusion Criteria for non-EDE Classification:

- Tear Evaporation Rate (TER) < 110 (TBC)

For patients who have one eye meeting EDE criteria, and other eye meeting non-EDE criteria, their Schirmer score will be used to determine the classification. If their Schirmer score is >10 in both eyes, they will be classified in the EDE group.

7.1.2. Exclusion Criteria

The following are criteria for exclusion from participating in the study:

1. Schirmer test (with anesthesia) ≤ 2 mm in either eye at Screening;
2. Patients who are currently using topical ocular medication or have used topical ocular medication within 2 weeks of the Screening visit. Patients who are being treated bilaterally with a marketed artificial tear for dry eye can be considered, provided they discontinue use at the Screening visit;
3. Any active anterior segment disease excluding blepharitis;
4. 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;
5. History of epilepsy or migraines exacerbated by flashing, strobe-like lights;
6. Rigid or soft contact lens wearer, including orthokeratology;
7. History of eye surgery within 6 months prior to enrolment in the study;
8. Previous corneal refractive surgery;
9. Known allergy or sensitivity to the study product(s) or its components;
10. Females who are pregnant (self-report), nursing, or planning a pregnancy.

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 an adverse event that is related to the study eye drops and/or which, in the Investigator's or Sponsor's opinion, requires withdrawal of the participant;
- Participant voluntarily withdraws consent from the clinical trial (i.e. Revocation of Consent);
- Participant is lost to follow-up, or relocates and cannot attend the clinic;
- If a participant is not compliant with the clinical trial requirements and instructions e.g. visit schedule;

- Repeated protocol violations/deviations.

7.3. Withdrawal and Follow-up Procedure

Participants who are permanently withdrawn from the study should be seen as soon as possible after stopping use of the study eye drops for a final visit to assess participant safety and to return any unused study eye drops. This may be done at a routine clinic visit or an unscheduled visit if it occurs between routinely scheduled visits.

7.3.1. The Final Study Exit Visit

Where possible, the data requirements for the final study exit visit are the same assessments as for the 4 week assessment (Visit 4c) shown in Table 5. However, the minimum data requirements include:

- Visual acuity
- Slit-lamp biomicroscopy (ocular redness, corneal and conjunctival staining)

For withdrawal of consent, a 'Revocation of Consent' document should also be signed, if possible.

7.3.2. Lost to Follow-up

A participant will be considered lost to follow-up, after three documented and failed attempts have been made to contact the participant – two phone calls and one written. Any contact should attempt to gain the following information:

- reason participant has not returned to clinic
- safety (previous/new adverse events status), and
- concomitant therapies.

7.3.3. Event Follow-up

If a participant has experienced an adverse event that is continuing at the end of the study participation, the event is marked as ongoing. The Investigator should ensure appropriate follow-up care is arranged/provided to the participant as appropriate.

If an adverse event has occurred and is continuing, the participant should be followed until the event has resolved, or stabilised if there is no chance of improvement. Source notes and the reporting form should be updated as

appropriate, and the information forwarded to the Sponsor/HREC/TGA as necessary.

7.3.4. Whether and How Participants are to be Replaced:

Participants who experience an adverse response during the course of the study, that requires early discontinuation from the study, will not be replaced. Participants who are not suitable at Screening will be replaced, until the enrolment target is reached.

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;
- If the Sponsor 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 ‘001’.

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 conditions.

- ***Slit-Lamp Biomicroscopy:*** A specialised microscope with its own light source is used to examine the anterior eye including the Meibomian glands.

- ***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.

- ***LipiView® Ocular Surface Interferometer (TearScience®):*** Will be used to measure the absolute thickness of the tear film lipid layer. 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.

- ***Questionnaires:*** Questions assessing eye symptoms and product usage will be administered on paper forms.

- ***Participant History File:*** Created at commencement of study and maintained throughout the trial. Contains relevant references to participant's medical history (both prior to participation in the trial and ongoing throughout the trial); and contains details of any problems encountered during the trial (either through observation by the investigator or as volunteered by the participant).

9.2. Non-Standard Equipment and Procedures:

Non-standard procedures that will be performed include:

- ***Tear Evaporation Rate:*** The Vapometer is a closed chamber device which is used for measuring transepidermal water loss.
- [redacted]
- ***Photography/Video:*** A photograph of the eye will be taken at the first visit, and photographs and video recording of any interesting/unusual findings may also be made for documentation and/or follow-up purposes at other visits.

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 Study Eye Drops

The study eye drops will be dispensed to each randomized subject at Visits 2a, 3a and 4a. Run-in product will be dispensed at Visits 1, 2c and 3c. Each subject will be instructed by the investigator to instill 1 to 2 drops in each eye, as needed, but at least 2 times daily. The same vial can be used for both eyes, and should be used one time only. The vial should be discarded after each usage. If the subject is concurrently using approved Restasis or glaucoma therapy drops during the study and run-in period, they should be instructed to wait a minimum of 15 minutes between drop instillations. Subjects should be instructed not to instill any eye drops within 3 hours prior to their scheduled study visits.

10.2. Study Product Storage and Accountability

10.2.1. Storage Requirements

The study product must be stored in a secure area. Only assigned study personnel authorized by the investigator may have access to study product. Study product can be administered only to subjects entered into the clinical study, at no cost to the subject, in accordance with the conditions specified in this protocol.
Study product must be stored at room temperature.

10.2.2. Accountability

A Study Product Tracking spreadsheet is used for keeping track of who, where and when study product has been issued or dispensed to.

- ***Receipt of Study Product:*** Once invoice has been checked, the study eye drops will be entered into the Study Product Tracking spreadsheet.

- ***Issue of Study Product to Clinical Trial Participants:*** The Optometrist is responsible for documenting the dispensing of the study product on the participant case record form and in the Study Product Tracking spreadsheet.
- ***Disposal of Unused Supplies:*** Instruction will be obtained from the sponsor as to how to handle returned, unused study product.

10.3. Concomitant Therapy

10.3.1. Permissible Medications/Treatments

Therapy considered necessary for the subject's welfare may be given at the discretion of the investigator. Systemic medications that **do not** cause or affect dry eye, dry mouth, changes in vision or other ocular changes are considered permissible medications. No topical ocular medication is allowed during the study, except for subjects meeting all inclusion and exclusion criteria for their use of monotherapy for glaucoma or OHT, or RESTASIS cyclosporine ophthalmic emulsion drops. Subjects using monotherapy for glaucoma or OHT, or RESTASIS, should continue to use their drops at the same dose and frequency for the duration of the study. If the permissibility of a specific medication/treatment is in question, please contact [redacted].

10.3.2. Prohibited Medications/Treatments

Contact lens use is prohibited during the study. Subjects are not allowed to have any scheduled or planned ocular or systemic surgery or procedure during the study that in the investigator's opinion may inhibit the subject's study participation.

Subjects are not allowed to receive temporary or permanent occlusion or cauterization of the lacrimal puncta during the study. After Screening, subjects should not begin or stop the use of any systemic medications that may affect a dry eye condition or affect vision (e.g. may cause blurred vision, cataracts, or glaucoma). Sites should look up the potential adverse reactions of each medication to ensure they do not fall within these exclusionary drug families. In addition, subjects should not **begin** using any topical ophthalmic medications such as topical cyclosporines, ophthalmic steroids, or glaucoma drops while enrolled in the study.

The decision to administer a prohibited medication/treatment is done with the safety of the study participant as the primary consideration. When possible, [redacted] should be notified before the prohibited medication/treatment is administered

10.4. Participant Instructions

General instructions to all participants

- Contact the clinic immediately if problems are experienced or if they have any questions or concerns
- Use the study eye drops provided only as instructed over the course of the study
- Instill 1 to 2 drops in each eye, as needed, but at least 2 times daily
- The same vial can be used for both eyes, and should be used one time only. The vial should be discarded after each usage.

11. ASSESSMENT OF EFFICACY

11.1. Parameters

- Subjective comfort
- History
- Visual acuity
- Eye photo
- Tear evaporation rate
- Lipid layer thickness
- Tear break-up time
- [redacted]

11.2. Methods

Ocular comfort will be assessed by completion of paper-based questionnaires [redacted]

History (including medical and general health) will be recorded on the Participant History File at all visits.

Habitual visual acuity will be measured at each visit using standard letter charts.

A photograph of the anterior eye will be taken at the Screening visit only for participants who are eligible to continue into the randomization phase of the study. From the photograph, ocular surface area will be measured in order to calculate the absolute tear evaporation rate.

Tear evaporation rate will be measured using the Vapometer. 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. Three measurements will be taken for each eye under open eye and closed eye conditions. Each measurement will be recorded and the absolute evaporation rate will be calculated for each eye.

Tear lipid layer thickness will be measured using the LipiView Ocular Surface Interferometer. 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

Slit lamp biomicroscopy will be performed at each visit. This will be used to assess the following variables and rated using the CCLRU (Appendix II) and CIBA grading scales (Appendix III).

- Bulbar conjunctival redness
- Corneal and conjunctival staining (in conjunction with fluorescein and a Wratten 12 filter)

Tear break-up time (TBUT) will be performed with the application of fluorescein and a yellow barrier filter. A stopwatch will be used to record the first occurrence of true tear break-up, not just local thinning or tear film irregularity. Three consecutive TBUTs will be performed per eye and the time in seconds for each of the three measurements will be recorded.

[redacted]

12. ASSESSMENT OF SAFETY

12.1. Parameters

- Discomfort
- History
- Habitual visual acuity
- Biomicroscopy
- Corneal and conjunctival staining

12.2. Methods

Discomfort will be assessed using questionnaires and the Participant History File at all scheduled visits.

History (including medical and general health) will be recorded on the Participant History File at all visits.

Ocular examination using slit-lamp biomicroscopy will be carried out at baseline and at every visit. Ocular redness (bulbar) and corneal and conjunctival staining will be assessed and recorded using the CCLRU (Appendix II) and CIBA grading scales (Appendix III).

An optometrist will be available for the duration of the study. Participants will be advised to contact the optometrist immediately of any unusual event 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

The principal investigator, or designated personnel determined to be medically qualified by the principal investigator, will question the subject about adverse events. All adverse events will be documented.

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.

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 immediately cease use of the study eye drops and contact the clinic.
Non-serious adverse events should be recorded as part of Good Clinical Practice.

All Serious Adverse Events (SAEs) will be reported to the Co-Sponsor ([redacted]) within 24 hours of first knowledge of the event, even if the information is incomplete, using the SAE report form. This procedure is required regardless as to the causal relationship to the study eye drops and also relates to SAEs which are spontaneously reported to investigators from patients taking [redacted] products which are <u>not</u> being investigated as part of the study.

[redacted]

SAEs will also be reported to the HREC as per their reporting requirements and to other regulatory authorities as applicable under local regulations. This should be followed by a more detailed written report commenting on potential confounding factors, results of investigations, treatment required and outcome. The Sponsor

and the Principal Investigator should review the events in conjunction with the known information about the device, and make a determination as to whether the event is device-related or not.

The investigator agrees to provide written notice to [redacted] of any SAEs before publishing any such findings.

All other adverse events should be reported to the Sponsor no later than 10 days after the event.

12.4.1. Foreseeable Adverse Events

Risks associated with the use of the study products are likely to be allergic in nature and include:

- Eye irritation (<1%)
- Eye itching (<1%)
- Eye/eyelid swelling (<1%)
- Eye redness (<1%)

12.5. Follow-up

Participants who experience an adverse response during the course of the trial will be followed up until the condition resolves or the participant is referred to another practitioner. ***Permanent discontinuation:*** will occur when, in the optometrist's opinion (or ophthalmologist's, if participant has been referred), continued use of the study eye drops will be detrimental to ocular health.

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 6

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. The study may employ at least one interim analysis. Data will be investigated for quality using range checks and frequency distribution. Underlying distributions of variables will be tested. In general, variables measured on an interval scale with a sufficiently large sample size will be considered to follow a normal distribution. Details of statistical analysis are described in Section 13.1.3.

13.1.1. Number of Participants

Up to 40 participants will be recruited (approx. 20 EDE and 20 non-EDE subjects). This sample size was calculated on the basis of detecting a difference in:
tear evaporation rate between the eye drops of 36 gm^{-2}/h where the expected standard deviation of the measurement is 50 gm^{-2}/h, assuming an estimate of type 1 error α =0.05 and power of 80% for a two tailed test.

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 have commenced the study treatment will be included in the analysis dataset. Reasons and frequency distribution of participants discontinued at the Screening visit will be reported. The analysis of efficacy variables such as subjective ratings will employ only scheduled and evaluable visits. The analysis of safety variables such as adverse responses will include all visits, including all unscheduled visits.

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 between between visits and $p \leq 0.05$ will be considered statistically significant. . Multiple comparisons will be adjusted using Bonferroni's correction. Commonly used tests of significance at each visit may include paired t-tests and group t-test for parametric data and Wilcoxon sign rank test and rank sum test for non-parametric data or repeated measures Analysis of Variance (ANOVA) for parametric data to determine differences between within-subject factors. Ranked variables will be analysed non-parametrically using Friedman's analysis of variance or Wilcoxon Signed Rank test to determine differences. Paired categorical variables will be compared using McNemar's test and grouped categorical variables will be analysed using Chi-Square tests. Mann Whitney U test will be used to compare tear film lipidome between the eye drops.

13.2. Criteria for Termination of the Trial

The trial will be terminated upon completion of the final visit by the last active 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. Data from unscheduled visits will be used only for adverse response analysis. 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 are 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, the Sponsor and the Sponsor's representatives, 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 or as agreed with the Sponsor and/or the Principal Investigator. 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 or by an agreement with the Sponsor.

The Sponsor must retain essential documents for the periods as specified above per ICH GCP and per TGA for 15 years following the completion of a clinical trial. However, per TGA requirements, essential documents may need to be retained longer after consideration of the following: product liability and the potential need for sponsors of products to produce records at any time during, and possibly beyond, the life of a product in the event of a claim against the Sponsor 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

It is agreed between the Sponsor and the Investigator that deviations will be reviewed to determine the need to amend the protocol or to terminate the investigation. Justification for any changes must be provided.

Protocol amendments will be submitted to the Sponsor and 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, communicate with the Sponsor regarding any clinical trial issues or need for protocol modifications, 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 and Sponsor 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 of the devices received must be reconciled with the quantities of the device 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.)*

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best 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.

APPENDIX II

CCLRU GRADING SCALES

APPENDIX II: CCLRU Grading Scales

The CCLRU Grading Scale uses a 0-4 scale in 0.5 steps, as shown in the following table:

Table 7

Grade	Description
0	Absent
1	Very Slight
2	Slight
3	Moderate
4	Severe

The scale is to be used in conjunction with the colour photographs as a standard to compare the observed finding and grade accordingly.

APPENDIX III

CIBA GRADING SCALES

APPENDIX III: CIBA Grading Scales

SLIT-LAMP QUANTIFICATION CHART

BIOMICROSCOPY SIGNS

Bulbar Redness

0 = **None:** White and clear
1 = **Trace:** Regional hyperemia
2 = **Mild:** Diffuse hyperemia
3 = **Moderate:** Marked regional or diffuse hyperemia
4 = **Severe:** Diffuse episcleral or scleral hyperemia

Epithelial Staining

0 = **None:** No staining
1 = **Trace:** Regional superficial stippling and/or foreign body tracks
2 = **Mild:** Regional or diffuse punctate staining and/or F.B. tracks
3 = **Moderate:** Dense coalescent staining and/or abrasions
4 = **Severe:** Epithelial loss, or full thickness abrasion

Conjunctival Staining

0 = **None:** No staining
1 = **Trace:** Minimal regional staining
2 = **Mild:** Regional or diffuse punctate staining
3 = **Moderate:** Significant dense coalescent staining
4 = **Severe:** Severe dense geographical staining